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SEROLOGICAL AND ALLERGIC REACTIONS WITH SIMPLE CHEMICAL COMPOUNDS*

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THE subject of this paper might seem to bear no relation to the topic of parasitism, under consideration in this session, were it not for the fact that similar principles are involved in the exaggerated reactions to chemical agents — known as allergic or idiosyncratic — and in certain responses of the animal body consequent upon invasion by infectious microorganisms. This connection has been brought to light through the development of serological research; and at the same time an ever-increasing array of clinical pictures has been found, or assumed, to belong in the field of allergy, being as multiform as hay fever, asthma, migraine, mucomembranous colic, purpura and various cutaneous manifestations including eczema, urticaria and angioneurotic edema.

The knowledge of exceptional untoward effects of drugs, or disturbances resulting from contact with plants or ingestion of food must be as old as medical experience and histories of such cases date from early times. But the phenomena of idiosynerasy, in particular, drug idiosynerasy, which I propose to discuss in some of its phases, remained wholly inexplicable until the memorable discovery of anaphylaxis. Here it developed that animals treated with a minute dose of a serum died when injected again after a suitable interval with a small amount of the same material. While the work of Behring, Kitasato, and their followers had shown that the administration of toxins or bacteria affords protection or causes increased resistance, an essentially similar mechanism now was seen to induce specific hypersensitiveness to proteins. To all appearances this was a clue to the understanding of drug idiosynerasy. In both cases very small quantities of otherwise innocuous substances produce severe effects in sensitive individuals, and in both instances the sensitivity is strikingly specific.

Still there are significant differences between the two conditions which at once seemed irreconcilable and which led some to deny any essential relation. In the first place the incitants of drug allergy are substances of low molecular weight having as a class, for all one knows, no antigenic activity, in distinction to antigenic proteins of large molecular size that incite the production of antibodies and induce anaphylaxis; secondly, the anaphylactic state can be set up regularly with practically any foreign protein, whereas, as a rule, only a few individuals who come in contact with the drugs in question acquire hypersensitiveness. It was believed, furthermore, that hypersensitiveness in man may occur without previous contact with the exciting agents, a proposition which is difficult to prove conclusively and is rather discounted at present.

The most impressive of these arguments is that relating to the lack of antigenic capacity in the substances causing drug allergy. In this regard the suggestion had been advanced years back that the substances may combine with proteins within the body to form antigens. Yet this hypothesis, at the time based chiefly upon the observation that proteins, treated with iodine, engender immune sera reacting specifically with iodoproteins, did not carry conviction. It was in fact not possible by immunization with iodoprotein to produce hypersensitiveness to iodine and the antibodies so obtained are not specific for iodine, but for the diiodotyrosine groups contained in the altered protein. The hypothesis, however, subsequently gained support from a series of studies on artificially conjugated antigens.

In essence these investigations[1] established that simple chemical compounds can be converted into antigens by being attached to proteins. To effect this, the method that so far has proved the the most convenient is the preparation of azoproteins, by coupling proteins with diazonium compounds, according to the procedure employed in synthesizing common azodyes. For instance, upon diazotization of one of the three aminobenzoic acids, say the para compound, and coupling it to proteins a conjugate is obtained which on injection into rabbits causes the formation of antibodies stamped with the pattern of paraaminobenzoic acid. These antibodies react with all azoproteins made from this acid and differentiate them and other azoantigens, even those prepared with ortho- or meta-aminobenzoic acid. Results obtained with a rather wide variety of

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substances were conformable. There now arose the question whether, as had been presumed, the simple compounds, firmly attached to protein, themselves react with the antibodies, or if the chemically modified protein must take part in the reactions, the latter being the case with such altered proteins as oxidized protein, or the iodized derivative already mentioned. A decision in the matter was reached in the following way. The formation of precipitates by the interaction of immune serums and soluble antigens, it was observed long ago, is prevented, or the quantity of the precipitate diminished, if the proportion of antigen is sufficiently increased. The phenomenon depends upon the formation of a soluble compound containing much antigen in relation to the amount of antibody. In dealing with "synthetic" conjugated antigens it seemed not unreasonable to ascertain whether the substance attached to protein and supposed to react with the corresponding antibody could by itself interfere with and thus inhibit the precipitation of a conjugated antigen by the homologous antiserum. If so, the interaction between the simple substance and the antibody would be demonstrated. The outcome of the experiment was affirmative.[2] Accordingly, in the example referred to, the precipitation of para-benzoic acid azoprotein is inhibited by addition of a neutralized solution of para-aminobenzoic acid. Examination of numerous cases showed that the specificity of the inhibition reaction is of the same order as that of precipitin reactions and there was no other satisfactory explanation than that the inhibiting substances combine with the antibodies and so block their union with the complete antigen.

A similar effect was demonstrable in vivo. Guinea pigs injected with an azoprotein become anaphylactic and are shocked by reinjection of the same antigen or by other azoproteins prepared with the same diazonium compound. If the latter is coupled not to protein but to a phenol, as resorcinol or tyrosine, the resulting dye will usually not elicit anaphylactic shock but will afford protection to the sensitized animal against a subsequent injection of the azoprotein.

Interesting experiments devised to demonstrate the specific combination of the azodyes with correlated antibodies were described by Marrack and Smith,[3] and Haurowitz and Breinl.[4] An azodye made by combining tyrosine and diazotized para-amino-phenylarsenic acid was mixed with antibody globulin separated from an homologous antiserum, and the solution was placed in a dialyzing apparatus in order to determine the ratio of azocompound bound by the globulin, to free azodye. This ratio was found to be much greater than in control tests with globulins from normal serum or with azocompounds not related to the immune serum.

In general, the union of antibodies and substances of low molecular weight is not accompanied by a perceivable change, yet, with certain azodyes of low formula weight, visible reactions occurred.[5] These compounds were obtained by combining diazotized aminoanilic acids, such as aminosuccinanilic or aminosuberanilic acid with resorcinol. Upon adding immune serums prepared with anilic acid antigens to solutions of the homologous simple dyes, precipitation occurred just as in common precipitin tests with proteins or bacterial polysaccharides and the reactions were observable with antigen dilutions even as high as 1:1,000,000. The same azocompounds produced typical anaphylactic shock in fractions of milligrams, a result once more confirming the relationship between specific precipitation and anaphylactic shock. The peculiarity of the substances is probably connected with a tendency to form colloidal solutions, indeed aged solutions proved to be more suitable for the experiments than those freshly prepared. But the behavior of the anilic acid dyes is not unique inasmuch as similar though slight reactions have been noticed with other azodyes.

In summary we may say that one obstacle to the understanding of drug allergy has been removed since we have learned that immunological reactions are not limited to proteins but take place as well with synthetic substances of simple composition lacking antigenic activity. Moreover, such substances—under special conditions—may, depending upon an antibody mechanism, elicit allergic reactions in the animal. A major difficulty remains. In the experiments outlined, antibody formation and the anaphylactic state were induced by conjugated proteins. How are effects of this sort brought about by synthetic chemicals or simple natural drugs where the chemical properties would not immediately suggest that they enter readily into firm combination with proteins?

That drug allergy, despite cases of seemingly spontaneous origin, may be acquired by contact with the excitants had been verified amply by clinical observations; elucidation of the mechanism involved could hardly be expected other than through experiments. This approach did not appear highly promising at first as there was reason to believe that the condition depends on idiosyncrasy, that is, a peculiarity—probably constitutional—of certain individuals. Nevertheless, Nestler (1904) and Low[6] (1924) were able to sensitize some human beings to extracts of primrose, a plant at times causing persistent, irritating skin eruptions, and a similar result was obtained with an alkaloid contained in satin-wood, another excitant of allergic skin affections. The experiments with Primula were repeated on a broader scale by Bloch and Steiner-Wourlisch[7] with almost invariable success. Hence, while under natural conditions only a few

among the many who handle Primulas become sensitive, intense treatment with concentrated extracts was shown to sensitize practically any individual and, in this case at least, a typical instance of idiosynerasy, as Bloch remarks, was proved to be an acquired allergic state.

In guinea pigs, likewise, regular results were obtained with Primula extracts, and also with the isolated crystalline active substance, primine, of the composition $C_{14}H_{18}O_3$, and similar effects have been observed lately by Simon, Simon, Rackemann and Dienes[8] on application of poison ivy. The toxic principle in this plant is the same as in Japanese lacquer. The substance, urushiol, was found by Japanese workers to be a catechol with an unsaturated side chain of the formula $C_6H_3(OH)_2C_{15}H_{27}$. By applying it to the skin of guinea pigs we had no difficulty in producing sensitization.

Among other substances that have been tested in animals with positive results mention may be made of arsphenamine,[9] known upon occasion to cause accidents on therapeutic administration, phenylhydrazine,[10] and para-phenylenediamine,[11] widely used for dyeing pelts, which gives rise to skin eruptions in persons wearing furs, and asthma in dyers and furriers. Here, the affinity for proteins — utilized in the dyeing process—may well account for the formation of antigenic products in vivo.

However, the experiments carried out with various chemicals were in part not clear-cut, or not easily reproducible. An illustration of the difficulties is the experience of Sulzberger and Mayer.[12] While these investigators had secured definitely positive results with arsphenamine in a laboratory in Germany, they were unable to sensitize guinea pigs in New York, even though they used the same technic and the same brand of the drug as before. Similar inconsistencies were encountered in the experiments with phenylenediamine. Further studies led Mayer and Sulzberger to the opinion that the diet is of significant influence in determining the outcome of the experiments, as green fodder was said to render the animals resistant, dry fodder having the opposite effect while Simon[13] recently reported the necessity of vitamin C in the diet. But it appeared that, not counting individual variations, there may be other unknown factors responsible for the observed discrepancies. Still greater uncertainty obtains as to the possibility of sensitization, after the fashion of passive anaphylaxis, by injecting the serum of hypersensitive patients into animals. This claim, advanced by several authors, is the more questionable for the reason that even transfer of drug sensitiveness from man to man succeeds only exceptionally, if at all, in contrast to that other class of human allergies of which sensitivity to pollens is an example, where there are antibodies which sensitize the skin of normal individuals. It is not surprising from the foregoing that in current textbooks the matter of drug hypersensitiveness in animals is briefly dismissed or for the most part treated with scepticism.

In taking up the subject[14] it was the first concern of Dr. Jacobs and myself to find suitable, readily accessible substances and to establish a method that would furnish consistent results. Aided by previous studies of Kolle,[15] a technic answering the purpose was found in repeated intracutaneous injections of very small quantities of the chemicals or application of solutions to the intact surface of the skin. In this way definite sensitization effects were obtained with numerous and diverse substances. As examples of very active compounds, I may cite paranitrosodimethylaniline and 2.4 dinitrochlorobenzene. For instance, in a representative experiment a lot of six guinea pigs was injected intracutaneously for 8 days, each time with 1/400 milligram of dinitrochlorobenzene, 1/50 milligram in all. After a rest period of 3 weeks, a drop of a 1 per cent solution in oil was spread on the skin. Some hours later reactions became apparent, and on the following day the treated sites showed pale to intensely pink coloration, at times with a distinct thickening of the inflamed area. The same treatment caused no change or a negligible one in the skin of normal controls. In a number of experiments made in this or a similar manner the result was definitely positive with sixty-nine animals and doubtful with four only. Hence as regards regularity the method compares with the standard anaphylaxis experiment and the comparison extends to the specificity of the reactions, the duration of the allergic state and the small quantities of substance, e.g., 1/250 milligram, which are sufficient to induce an increase in sensitivity. A significant difference between the two conditions lies in the fact referred to above that, in drug allergy, direct evidence for the presence of antibodies is still wanting. Yet, the existence of some sort of antibodies, perhaps fixed in or on the cells, is not disproved by the failure to demonstrate them with the usual methods, and antibodies would indeed most readily explain the spreading of sensitiveness all over the skin after injection into one site.

The choice of dinitrochlorobenzene was suggested by the frequent occurrence of allergic skin eruptions in industrial workers exposed to the compound,[16] and our sensitization experiments have been confirmed in human beings.[17] The skin lesions in man are similar in character to those produced in guinea pigs, but there is a striking disparity in degree and in the range of individual sensitivity. Tested in the same manner by means of putting drops of alcoholic solutions in decreasing concentrations

on the skin, well sensitized guinea pigs were found to react to dilutions of 1:100 and 1:1000 like the majority of allergic persons. But some people give reactions with solutions of 1:100,000 or even 1:1,000,000 while the experimental animals have never shown so high a degree of sensitivity and so much individual variation. Anticipating genetic studies this would indicate wider constitutional differences in man, in contrast to animals, relative to the predisposition to sensitivity either in general or concerning particular compounds. With less active substances or when exposure is not so intense as, for example, among factory workers, only occasionally may a person become affected and such a case will be set down as idiosyncrasy. Consequently, restricting ourselves at this moment to the drug allergies under discussion, we may, with Doerr, conclude that only gradual differences exist and that no sharp line can be drawn between normal and idiosyncratic individuals. A contrary view is held concerning another type of allergic affections—hay fever, asthma, nutritional eczema—characterized by Coca as due to a special sort of antibodies and depending strictly on heredity.

In the further course of our study various substances were examined in order to ascertain, if possible, relationships between chemical properties and sensitizing capacity. This point was touched upon some years ago by R. L. Mayer who found that a number of aromatic substances, supposedly related to phenylenediamine in that they are changed into quinoid compounds by oxidation, evoke allergic responses in persons sensitive to the diamine. The subject, nevertheless, is still in a state of obscurity so that the excitant drugs and chemicals have recently been pertinently described by a writer of authority as "a whole series of chemical compounds which seem to have no characteristic or common structure". The observations on 2.4 dinitrochlorobenzene led to the question precisely why this compound should be a powerful sensitizing agent and suggested the examination of allied substances.

TABLE 1

Substance	K*	Reaction with Aniline‖	Sensitization
1:2:4 Chlorodinitrobenzene	0.110 (0°); 3.26 (15°, eth.)	+	Positive
1:2:4 Bromodinitrobenzene	1.89 (15°, eth.)	+	Positive
1:2:4 Iododinitrobenzene	0.455 (15°, eth.)	+	Positive
1:2:4 Fluorodinitrobenzene	686.0 (15°)	+	Positive
1:4:2:6 Dichlorodinitrobenzene	0.0248 (0°)	+	Positive
1:3:4:6 Dichlorodinitrobenzene	1.20 (0°)	+	Positive
1:2:4:6 Chlorotrinitrobenzene	Very great† (0°)	+	Positive
1:3:5 Dichloronitrobenzene	Reaction irregular‡	—	Negative
1:4:2 Dichloronitrobenzene	0.00000297 (0°)	—	Negative
1:2:4 Dichloronitrobenzene	0.0000183 (0°)	—	Negative
p-Chloronitrobenzene	0.000000987 (0°)	—	Negative
p-Dichlorobenzene	0.00019 (175°)	—	Negative
1:2:4 Trichlorobenzene	Very small§ (0°)	—	Negative
1:2:4:5 Tetrachlorobenzene	Very small§ (0°)	—	Negative
Hexachlorobenzene	Very small (175°)	—	Negative

*Constants from the literature for the velocity of decomposition of the substances by sodium methylate, or sodium ethylate (eth.) at the temperature indicated.

$$K = \frac{x}{A\ (A-x)t}$$

(A = initial concentration, x = Cl liberated, t = time.)

†Velocity too great to be measured.

‡Formation of azoxy compound.

§Value found to be very small, less than or of the same order as that for 1:2:4 dichloronitrobenzene.

‖The symbol + designates almost complete liberation of halogen (more than 90 per cent), and the symbol — indicates that no or very little (less than 5 per cent) halogen was replaced.

According to the theory of benzene substitutions more than 90 chloro- and nitro-substitution products of benzene are possible and most of these have been synthesized. Seventeen of the compounds were examined for sensitizing capacity, and seven yielded distinctly positive effects. It being known that 2.4 dinitrochlorobenzene contains a labile chlorine easily detached by alkali and that it correspondingly forms substitution compounds with organic bases, phenols, thiols, and amino acids, it was obvious to compare the results of the animal experiments with the chemical data on the lability of the substituents in the substances examined. These can be grouped according to whether alkali splits off a chlorine atom, or a nitro group. The reaction constants for the first group are assembled in table 1.

As is seen at a glance, the figures indicating the velocity of decomposition by alkali in alcoholic solution are much higher for the sensitizing compounds. In the second group (table 2) there was an exception. The two trinitrobenzenes, the 1.2.4 and the symmetrical (1.3.5)

trinitrobenzene, alike in chemical structure except for the position of one nitro group, showed a marked difference in the animal experiment. Thus, in several batches of guinea pigs injected intracutaneously with the 1.2.4 compound all showed definite or at worst slight allergic reactions while identical treatment with the symmetrical compound failed to produce any signs of sensitization. Yet, in the latter case the reaction constant is greater than that of several "positive" substances. This inconsistency vanished when the reactivity was tested not with alkali but with an organic base. Using aniline, it was now found that all positive substances, but none of the negative ones, gave stable substitution compounds. In particular, 1.2.4 trinitrobenzene gives off nitrous acid and is substituted to yield a dinitrodiphenylamine, while the symmetric isomer forms a loose molecular compound from which it can easily be recovered.[18]

TABLE 2

Substance	K_o^*	Reaction with Aniline§	Sensitization
1:2:4:5 Dichlorodinitrobenzene	0.326	+	Positive
1:3:2:5 Dichlorodinitrobenzene	0.145	+	Positive
1:2:4 Trinitrobenzene	Very great†	+	Positive
1:3:5 Trinitrobenzene	1.57	—	Negative
m-Dinitrobenzene	Reaction irregular‡	—	Negative

*Constants for the velocity of decomposition of the substances at 0° C by sodium methylate.

†Velocity too great to be measured.

‡Formation of azoxy compound.

§The symbol + indicates the formation of a substitution compound and the symbol — formation of an addition compound.

Assuming the apparent parallelism between chemical and allergic reactivity to be significant, one should be able on chemical grounds to detect sensitizing compounds. Indeed, the expectation that benzyl chlorides would have the capacity of sensitizing by virtue of a loosely bound chlorine atom was fulfilled and the results obtained with benzyl chloride and several derivatives were quite similar to those described above. It was not difficult, then, to find another group of sensitizing substances, namely the acyl chlorides, generally used for acylation of amino- or hydroxyl groups. The skin sensitization incited by means of para-chlorobenzoyl chloride (or benzoyl chloride) again took the regular course, the treated animals showing superficial dermatitis on application of oil solutions. Concurrently an unusual effect was seen on intracutaneous administration. Injections of small quantities—1/100 mg.—dissolved in oil were followed by reddening and intense swelling over a large area, with central necrosis, resembling the lesions in animals repeatedly injected with proteins.

We proceeded then to test a compound prepared by combining serum protein with chlorobenzoyl chloride. On intravenous injection of this acyl protein, guinea pigs sensitized intracutaneously to the chloride died, with the characteristic symptoms of anaphylactic shock. The same treatment, therefore, had induced skin sensitivity of the contact dermatitis type and, on the other hand, anaphylaxis such as is elicited by natural or altered proteins.

In these experiments anaphylactic effects ensued following injection of a conjugated protein in analogy to our results on sensitization with azoproteins. But it is a point of importance that we now know an instance where sensitization as well as anaphylactic shock can be produced by a synthetic chemical, i.e., arsphenamine. The somewhat controversial literature we need not consider, and it will suffice to note that by a special mode of treatment we were able to sensitize guinea pigs to arsphenamine so that, in a large proportion of the animals, acute anaphylactic death followed intravenous injection of the substance.

Clearly, the results obtained with substituted benzenes and acyl chlorides afford conclusive evidence for the view that sensitization with simple compounds may result because of the formation of antigenic conjugates in the animal.* Several problems require further investigation. In the cases in which the formation of conjugates seems indubitable, we are not sure about the nature of the components, derived from tissues or body fluids, which serve to confer antigenicity upon the excitants, since recent studies indicate that nonprotein substances, such as carbohydrates, alone or linked to lipoids, may be endowed with antigenic activity. More serious difficulties may be encountered in the instances where experimental data are lacking, there being numerous excitants of human allergy with which one has not been able, so far, to sensitize animals. And, as remarked before, often the chemical composition and properties of the substances reveal nothing obvious to allow a sound opinion concerning the reactions that may give rise to composite antigens. Yet there is always the possibility of chemical changes in the body preceding the union, and it should be considered that with certain substances mere admixture

*This should not be taken to imply that the process need be fully equivalent to immunization with conjugated proteins made in vitro; for instance, the mechanism may differ in that conjugation occurs within cells (18a).

with proteins was found to be sufficient for the formation of loose antigenic combinations.[19] That such processes might play a part in sensitization is suggested by the recent report of Haxthausen[20] on allergy in human beings following treatment with metal salts in combination with a foreign protein.

Another problem relates to the special role of the skin, repeatedly noticed both in sensitization and allergic reactions to drugs. This appears from the fact, already pointed out by Low, that sensitivity to poison ivy or Primula, as a rule, does not involve the mucous membranes. Likewise in animals, administrations by routes other than the intracutaneous proved less effective or not at all successful in eliciting skin sensitivity.[21]

In spite of all the open questions it may be taken as established from the foregoing that drug idiosynerasy, in many instances at least, comes into the same category as anaphylaxis.

There doubtless exist material differences, as viewed from clinical and theoretical angles, between various types of human allergy, conditional upon the nature of the exciting substances, the tissues involved in sensitization and allergic response, and factors—constitutional or otherwise — peculiar to the individual. Widespread, and occurring in many shapes and disguises, allergy is a concomitant of infections, a predominant source of industrial disease; it causes discomfort as in hives and serum sickness, or serious illness as with asthmatics; it may be associated with the presence of readily demonstrable antibodies while in other cases the elucidation of its mechanism still awaits patient experimentation. Yet we have gone far enough to regard with reasonable assurance idiosynerasies and allergic affections in general as manifestations of the very comprehensive and remarkable biologie phenomenon of adaptation, namely the adaptation of the organism to chemical agents by means of specific antibodies circulating or fixed in tissues. If successful, this mechanism guards against infectious disease but when it miscarries it induces sensitivity to minute quantities of proteins or simple chemical compounds. This, in short, sums up the substance of our present knowledge.

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21. Sulzberger, M. B.: Arsphenamine hypersensitiveness in guinea pigs; experiments demonstrating role of skin, both as originator and as site of hypersensitiveness. Arch. Dermat. & Syph. **22**:839, 1930. (*Vide* Bloch, Simon, quoted above.)

DISCUSSION

Dr. Sanford B. Hooker, Boston: I appreciate this honor, Dr. Zinsser, and I shall be very brief.

There is nothing in the matter of Dr. Landsteiner's paper that lends itself to any controversial discussion. What Dr. Landsteiner says in public he can prove. He has made a very convincing addition to our understanding of one of the many different kinds of allergic reactions.

There is one question that I should like to ask, if it is permitted, which may have some theoretical importance. I do not know that your experiments have gone far enough to allow you to answer the question, which is this: In these animals that were rendered anaphylactic by the injection of this simple benzoate of chloride, was it possible passively to transfer the epidermal sensitiveness?

Dr. Landsteiner: We have not had definite results as yet. We are trying to examine this question. I think it ought to be possible to transfer passively the anaphylactic sensitiveness, because it is exactly the same as when you inject a protein.

THE TREND OF PREVENTION, THERAPY AND EPIDEMIOLOGY OF DYSENTERY SINCE THE DISCOVERY OF ITS CAUSATIVE ORGANISM*

BY KIYOSHI SHIGA, M.D.†

THE discovery of the dysentery bacillus had stirred my young heart with hopes of eradicating the disease and saving the sufferings of about one hundred thousand cases that occurred yearly in my country at that time. Thirty-eight years have passed since this stirring event. Many thousand people still suffer from this disease every year, and the light of hope that once burned so brightly has faded as a dream of a summer night. This sacred fire must not die out.

I recall an address by Dr. Simon Flexner, my esteemed friend for many years, delivered some years ago at the Commencement of Cornell University Medical College: "The only distinction between 'clinical' and 'laboratory' science is that the former is more difficult to attain." In the same sense I may say that practical application is more difficult to attain than the search for the causes of disease.

My interest has always been focussed on studies of dysentery and I have followed closely the progress made by others. Today I wish to discuss briefly the bacillus, the therapy, the epidemiology and the prevention of dysentery in Japan.

I. NOMENCLATURE OF THE DYSENTERY BACILLUS

Many meritorious researches on dysentery bacillus made by Flexner and Strong in Manila, and Kruse in Germany should particularly be mentioned. A large number of variations and types have been reported since then and they are included under the name of dysentery bacillus. When the bacillus was discovered there were only bacillary and amebic dysenteries. Just as the natures of the causative organisms of the two are different, so the symptoms and modes of infections are entirely dissimilar. Consequently therapy and prevention must be instituted on different bases. For instance, in amebic dysentery ipecacuanha was thought specific at first and then emetin was discovered and finally, at present, yatren has been introduced. On the other hand, except for antitoxin, no specific method of treatment has been found for bacillary dysentery.

Strains of the dysentery bacillus discovered and studied by many investigators have been called by many different names depending upon differences in immune reactions or in fermentation of various carbohydrates. Some strains bear the names of the discoverers, or the places where the discoveries have been made, while others bear signs and symbols. They amount nearly to more than one hundred, and it would be almost impossible to remember them all. Among those who have attempted to systematize and classify the confusions of the nomenclature, Hiss and Russell stand out above all the rest. They classified the bacillus into four types according to its characteristics of toxin production and its affinity for mannite and carbohydrates. One is known as the Shiga type and the other three belong to so-called Flexner types. This classification is very convenient and appropriate.

In recent years other types of the dysentery bacillus have been reported, which could not very well be included in the foregoing classification. One is the Schmitz bacillus and the other is the Kruse-Sonne bacillus. In Japan the former had been known long before it was described by Schmitz. It was in 1907 that Dr. Ohno studied 5 strains of it and described its biologic characteristics very carefully. Since then many reports have appeared. (Tsurumi, 1 strain in 1908; Nishihara, 2 strains in 1913; Maruyama, 3 strains in 1916; and Shirai, 9 strains in 1916, and so forth.) On account of the nonacid and nontoxic nature of this type, I proposed to include it in the class of the metadysentery bacillus as will be seen in table 1. Some men think that the so-called Schmitz bacillus is an intermediate or transitional form between Shiga and Flexner bacilli or a variation of one or the other. Rutschko (Charkow, 1933) attempted to prove experimentally that the dysentery bacillus would undergo mutation in the intestines of chickens or cats. Whether or not the dysentery bacillus undergoes mutation to the metadysentery type or vice versa has not been conclusively proved.

Before discussing the Kruse-Sonne bacillus, I shall briefly describe dysentery and ekiri of children in Japan. We have many references to these diseases dating from early years. Ekiri (perhaps similar to the so-called summer diarrhea of children in the United States) in particular has been regarded as the most dreaded disease of children from its fulminating course and very high mortality. It begins with a sudden high fever followed immediately by convulsions and vomitings and, within 24 to 48 hours from the onset, the child passes away. Children of 4 to 6 years old are especially sub-

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ject to the disease, and the mortality is as high as 70 to 80 per cent. Dr. Ohara in 1914 isolated an organism and reported it as the causative agent of ekiri. Professor K. Mita in Kiushiu University during 1913 to 1918 isolated a strain from the stools of 21 cases out of 200 dysenteric children and named it the paradysentery bacillus. These two strains were found to be identical and the organism has been recognized as the causative organism of ekiri; it is known as the Ohara-Mita bacillus. Later it was proved to be identical with an organism described by Sonne in 1915.

During the past 38 years the causative organisms of dysentery have been almost completely investigated. But the nomenclature and the classification are still in confusion. Science is international and the nomenclature of the dysentery bacillus must also be scientific. It should not bear the names of the discoverers or the investigators. In 1933 I suggested the following classification. I believe that such a classification is appropriate and fulfills all the requirements of conditions that are presented.

I. B. Dysenteriae (representative strains are Shiga-Kruse bacillus); includes toxin producing and nonmannite fermenting organisms.

II. B. Metadysenteriae (representative strains are Flexner, Strong, Y, Ohno, Schmitz bacilli); includes mannite fermenting, nontoxin producing organisms.

III. B. Paradysenteriae (representative strains are Kruse-Sonne, Ohara-Mita bacilli); includes lactose fermenting, milk coagulating and variant colony forming organisms. (See table 1.)

TABLE 1

Type	I Dysentery Bacillus	II Metadysentery Bacillus				III Paradysentery Bacillus
	Shiga	(a) Ohno-Schmitz	(b) Flexner	(c) Y	(d) Strong	Kruse-Sonne, Ohara-Mita
Indolreaction	—	+	+	+	+	—
Mannite litmus	blue	blue	red	red	red	red
Lactose litmus	blue	blue	blue	purple	blue	red
Dextrose litmus	red	red	red	red	red	red
Maltose litmus	blue	blue	red	red	blue	(red or blue)
Saccharose litmus	blue	blue	red (blue)	blue	red	blue, then purple
Dulcite litmus	blue	blue	blue	blue	blue	blue
Katalose litmus	—	+	+	+	+	+
Milk	No coagulation					Coag. after 6-22 days
Dextrose	No gas-production					
Specific Toxin	+	—	—	—	—	—

II. TOXIN OF THE DYSENTERY BACILLUS AND ANTITOXIN TREATMENTS

Dysentery toxin by its nature belongs to the endotoxins and is a constituent of the bacillary body. At its death the toxin is liberated into the surrounding medium. Dr. Kawamura in my laboratory (1930) was unable to separate the dysentery toxin (Shiga type) into neutrotoxin and enterotoxin in animal experiments as well as in neutralization with the immune serums. Dysentery toxin produces antitoxin. This contradicts the idea we had hitherto held in regard to an endotoxin. Therefore we must accept the view that there are some endotoxins which produce antitoxins. The potency of the toxin as tested in animals places it next to tetanus and diphtheria toxin in strength. Tetanus toxin in a quantity of 1/10,000 cc. kills a mouse weighing 15 grams. Therefore 1 cc. of it kills 150 kilograms of mice. One cc. of diphtheria toxin kills 25 kilograms of guinea pigs, while one cc. of dysentery toxin kills 20 kilograms of rabbits.

Attempts to prepare a toxoid of dysentery toxin have not been successful so far and the hope of using a toxoid for prevention of the disease must be abandoned at present. Following the discovery of the bacillus, I prepared an immune serum with the organism and tested for the anti-infection titer. This serum was used for treatment of the disease with some favorable results. Later the toxin was found and antitoxin prepared. At the Serum Conference in Geneva in 1924, the method of testing and the unit of antitoxin were adopted. Thus the antitoxin treatment for bacillary dysentery has been recognized by the League of Nations. Hereupon it became necessary to determine the therapeutic value and dose of the antitoxin. During the three years between 1925 and 1927, I tried the antitoxic treatments at Keijo, and the results were reported to the League. In recent years the Shiga type of dysentery has almost disappeared in Japan proper. The most prevalent type has been metadysentery and the next paradysentery. Consequently it was impossible to try the serum treatments in Japan. Fortunately I was in a position to have opportunities for testing antitoxin of the Shiga type in the dysentery cases at Keijo.

In 1925, among the 22 dysentery cases hospitalized in the Keijo City Hospital, the Shiga type of organism was isolated from 19 cases

and metadysentery bacilli from 3 cases. In 19 cases the antitoxin containing 160 A. U. in 1 cc. was tried. In 1926, antitoxin containing 200 A. U. was tried on 12 cases of Shiga type, while in 1927 it was tried on 8 cases. This serum contained 300 to 400 A. U. The effects were favorable. The effective therapeutic units of antitoxin were found to be as follows: For mild cases, 3,000 to 4,000 A. U.; for moderate cases, 6,000 to 10,000 A. U.; and for severe cases, 10,000 to 12,000 A. U.

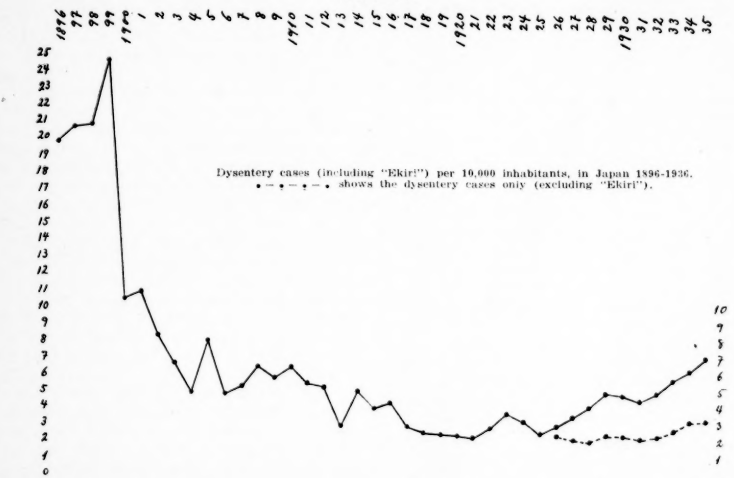
In the foregoing trials it was found that the dysentery antitoxin was especially effective in the treatment of mild and moderate cases, but for severe cases it was less effective. The reason why it was not effective in the severe cases may be explained by the fact that dysentery toxin acts upon the peristaltic centers of the intestinal walls, and, when paralysis of the intestinal walls has set in, the antitoxin has no power to neutralize the toxin. Experimentally it was found that a mild toxin stimulates peristalsis and causes diarrhea, but, when a strong toxin continues to act, it paralyzes the walls In the later stage the serum treatment becomes ineffective. Naturally it may be thought that a stronger antitoxin might be more effective. At the Kitasato Institute an antitoxic serum of 400 A. U. per cc. has been prepared, but it is at present not difficult to produce a serum containing 500 A. U. The serum treatment is not effective in meta- and paradysenteries.

Some other methods of specific treatment must be found for these types, but of its nature there is, as yet, no hint whatever.

III. EPIDEMIOLOGY OF DYSENTERY

At the time when the dysentery bacillus was discovered in 1898 there were 90,000 to 100,000 cases yearly in Japan. Since 1900, however, it decreased to 30,000 to 50,000 and since 1910 was still further reduced to 20,000 to 30,000. In the last few years it again increased to 30,000 to 40,000. The picture is still more vivid when the trend of the epidemics is shown according to the rate per 10,000 population. In 1898 it was 20.81 cases, and in the next year reached the record rate of 24.59, which suddenly dropped to 10.35 in 1900. After that year it gradually decreased with narrow fluctuations until 1920, when it reached the lowest level of 2.27 cases, then it again assumed the upward trend, and in 1935 was 7.07 cases (table 2). This increase is mainly explained by the fact that since 1923 ekiri has been added to the list of reportable diseases and cases of ekiri have been included in the category of dysentery (table 3).

TABLE 2


Dysentery cases (including "Ekiri") per 10,000 inhabitants, in Japan 1896-1936.
• — • — • — • shows the dysentery cases only (excluding "Ekiri").

The sudden decrease of dysentery in 1900 I do not claim should be attributed to the discovery of the bacillus. The gradual decrease since then must have been due to the adoption of a new policy of prevention based upon the discovery of the dysentery bacillus.

Next I shall touch upon the problem of carriers.

(a) Carriers of the Dysentery Bacillus: Dur-

ing the first period, between 1897 and 1910, of my studies of dysentery the majority of the patients were infected with the dysentery bacillus, Shiga type. Later the metadysentery bacilli, Flexner and Strong types, began to appear in

TABLE 3

THE FOLLOWING TABLE GIVES THE CONDITION OF DYSENTERY SINCE 1896

Years	Dysentery (Including Ekiri)	Ekiri (Only)	Cases per 10,000 Inhabitants
1896	85.876		19.74
1897	91.077		20.53
1898	90.976		20.81
1899	108.713		24.59
1900	46.255		10.35
1901	49.635		10.97
1902	36.996		8.08
1903	30.311		6.50
1904	22.772		4.82
1905	37.988		7.93
1906	22.277		4.59
1907	24.942		5.08
1908	32.809		6.38
1909	28.006		5.61
1910	31.960		6.33
1911	27.466		5.37
1912	25.667		4.96
1913	16.779		3.20
1914	26.127		4.87
1915	21.137		3.88
1916	22.452		4.07
1917	14.942		2.67
1918	13.997		2.46
1919	12.915		2.30
1920	12.728		2.27
1921	12.445		2.19
1922	15.134		2.62
1923	20.266		3.47
1924	18.646		3.17
1925	14.719		2.46
1926	17.132		2.83
1927	21.380		3.49
1928	11.418	13.773	4.06
1929	30.253	15.339	4.81
1930	29.680	16.091	4.61
1931	29.655	16.697	4.54
1932	32.251	18.345	4.86
1933	38.049	20.580	5.66
1934	42.952	22.033	6.30
1935	42.952	24.014	7.07

many cases, and in recent years the Shiga type practically disappeared, while the paradysentery bacillus began to appear in Japan. The Shiga type, however, is prevalent in Chosen.

Why has the dysentery bacillus been replaced by the meta- and paradysentery bacilli? How could such a phenomenon be explained? No convincing explanation can yet be offered. One may surmise that the number of cases of the dysentery bacillus is small because its carriers are few, and likewise the number of the meta- and paradysentery cases is large because the number of their carriers is large. Some men may reply that such a view inverts cause and effect. It may be so. The decrease or disappearance of the dysentery bacillus may be attributed to the law of survival of the fittest in commensal life in the intestines. I shall refer to it later.

Carriers were studied in Tokyo by the Metropolitan Policy Bureau in 1935. It was reported that, (1) 30 per cent of the convalescents were found to excrete the organisms for a long time. Some excreted it over 8 months; (2) 9.1 per cent of the familial contacts were found to be carriers. A study made in Kanagawa Prefecture has shown that there was a convalescent case that continued to excrete the organisms for 310 days. Dr. Kanasawa of the Navy Department reported convalescent cases that continued to be carriers for 196 to 324 days. There was a case also in the Navy that, by a reliable history, was shown to be a carrier for over 4 years. In the Navy, in attempts to detect the carrier, a proctoscope was used to find ulceration in the lower parts of the large intestine on the supposition that the ulcers were the hidden seats from which the organisms were liberated continuously. Treatment of the ulcer was expected ultimately to cure the carrier condition. Figures on dysentery cases show that about 75 per cent of the total are under the age of 10, while one quarter of the total carriers are found in the same age group. This indicates that children are less resistant to dysentery. The susceptibility of children can be explained by the physiologic function of the intestines. In the small child the functions of the small and large intestines are not yet differentiated. Consequently in dysentery or ekiri of children, both intestines are inflamed diffusely, while in adults the seat of the pathologic changes is usually confined to the colon and rectum. Exactly the same relations are demonstrable experimentally in rabbits. When the pathologic changes are limited to the large intestine the course is mild, but if the small intestine is also involved it is very severe. The high mortality and the fulminating course of ekiri are thus explained.

(b) Prevalent Types of Dysentery in the Carriers and Cases: We have mentioned the fact that there are many carriers of the metadysentery bacillus. Some have said that this represents only a relative increase due to the absolute decrease of the cases caused by the dysentery bacillus. But I rather think that the large number of carriers of the former account for the prevalence of cases of this type. The epidemics of the latter no longer occur because its carriers are not found. Why then have the carriers of the dysentery bacillus decreased while those of the other type have increased? I believe that dysentery bacilli are readily overcome by the colon bacilli in commensal association in the intestines. On the

other hand, the metadysentery bacilli, since they are closely related by nature to the colon bacilli, are able to maintain a commensal life with them. A large number of carriers naturally give rise to frequent epidemics. This supposition can be proved by comparing the length of life of dysentery, meta- and paradysentery bacilli in the intestines of experimental animals and by actual surveys of the frequency of each type of carrier in localities such as Keijo where cases due to dysentery bacillus are still prevalent. I shall have an opportunity to report on these points at some other occasion. It has been found by N. Ogata and then by T. Shibata that house rats are liable to become carriers of typhoid and dysentery bacilli. They believe that such a rat may be a source of dysentery infection. This view, however, is denied by Ido and others.

IV. PREVENTIVE VACCINATIONS

How shall we deal with the carriers which are the sources of dysentery epidemics? They are just as difficult to deal with as typhoid carriers. Suppression of carriers may be an important problem, but suppression of the cases is more feasible by immunizing or increasing the resistance of the general population by vaccination.

My study of preventive vaccination in dysentery falls into three periods. In 1899, vaccine was prepared by killing the bacilli with heat. I tried it on myself and was frightened by its severe reactions. This was enough and I never tried it on others. The next attempt was the preparation of a sero-vaccine. It was found that the reaction was less severe and resorption was rapid. This was used on tens of thousands of people, but it was abandoned on account of dangerous sensitization of the people. The last method attempted was oral vaccination. In 1907 animal experiments were made with the dysentery bacilli. This method was recommended by Besredka later and is now used widely.

The theories concerning the local or cellular immunity developed by oral vaccination are not in accord. Professor S. Mita found that a certain immunity was developed in the mucous cells of the intestine by oral administration of a protein substance. He called this phenomenon "habituation". When the mucous membrane of the intestines once takes up a certain protein it develops the power of resisting the same protein given subsequently. This property may be developed with pathogenic bacteria.

Oral vaccinations have been administered in Japan to hundreds of thousands of people during the last ten years. Though the results are claimed to be statistically favorable, careful consideration is needed before accepting them. It is necessary to investigate the methods of preparation and administration of the vaccine so as to secure better results.

V. CONCLUSION

Medical science has progressed steadily with miraculous success in some branches in particular. My whole life as a bacteriologist has been devoted to the study of dysentery, but in looking back over the field where I have sowed and toiled for 40 years, I cannot help thinking that the prospect of the harvest is not in sight. We must turn to a more hopeful field.

In tuberculosis, tuberculin, irritants and chemical therapies have been tried and failed. The prophylactic treatments with B. C. G. were tried in turn, but its effect is being watched with very cautious eyes. Diphtheria serum stands as the queen of all the serum treatments. But it did not reduce the diphtheria incidence very materially until antitoxin and toxin or anatoxin or the like were used for prophylactic purposes. Pasteur treatment had no material influence whatever on eradication of rabies until Umeno's preventive inoculations of dogs came into use.

We believe that the suppression of intestinal infectious diseases like typhoid and dysentery must rely upon the progress of modern public health practices. Here we find a beam of light directing us toward the goal which I had sought many years ago. It is a slow process to bring about the practical application of a scientific achievement. But it is a consolation and pleasure to think that we have devoted our efforts to humanity with an unselfish spirit of service, as Pasteur has said, "Until the time comes when you may have the great happiness of thinking that you have contributed in some way to the progress and good of humanity."

DISCUSSION

PROFESSOR F. F. RUSSELL, Professor of Preventive Medicine, Harvard Medical School: Professor Shiga said that it was 38 years ago when he first discovered the Shiga bacillus of dysentery. That was, of course, in 1898, in the days when we were engaged in the Spanish War. As a young medical officer in the Spanish War I was, of course, tremendously interested in learning of this discovery of Professor Shiga's.

We know that in the Civil War, diarrhea, dysentery, and chronic diarrhea were the principal causes of illness, of disability, and of wastage of troops. And so, at the beginning of the Spanish War we hoped, as the result of this discovery of Professor Shiga's that we would be able to control dysentery better than we had previously.

The methods which Professor Shiga used at that time were extremely simple, as, of course, were all the methods in bacteriology in 1898. He isolated many of the organisms that were discovered in dysentery cases and called those dysentery bacilli which were agglutinated by the serum of convalescent patients. That very simple and very exact method of work was the only method we had in those days,

the agglutination of dysentery bacilli in convalescent serum.

Thirty-eight years have passed, and during that time nothing has been taken away from this discovery of Dr. Shiga's, published in 1898. To be sure, we have added new authorities and new supporters, but everything that Dr. Shiga said at that time stands true today. And that is not true of all discoveries.

Professor Shiga has said that the application of these discoveries to practical prevention of disease is difficult. Of course it is difficult, and that is a thing which one does not always appreciate as Professor Shiga appreciates it. The application of a discovery to the protection of public health demands the cooperation of so many different authorities, so many different classes of workers.

In the course of time we have come to a realization that the enteric intestinal diseases are matters of sanitary engineering in their prevention, that is, sanitation, improvement in sanitary engineering, proper water supply, proper milk supply, proper disposal of excreta and proper treatment of sewage. All of these are essential, and their adoption has diminished intestinal diseases in an astonishing way.

The respiratory diseases, on the other hand, have not diminished. We have no simple method of control of respiratory diseases, and these diseases continue to prevail, as influenza does at the present time. With the intestinal diseases, however, as Dr. Shiga has said, the public health people have made tremendous progress in cutting down the prevalence of these diseases.

The classification of organisms which Professor Shiga proposed some years ago is an eminently practical and scientific one. Because we have been in the habit of talking about the Shiga bacillus and the Schmidt bacillus and other named bacilli, it will take some time to drop those names and to use a scientific nomenclature. That will come about in time, however.

The three types of organisms which have been added are all different from the true Shiga in that they produce no toxolysin. Yet clinically they are indistinguishable except perhaps in the severity of the disease.

In this country we have gone through a long experience in the study of dysentery bacilli. Gradually we have come to know, as in Japan, that dysentery is no longer the terrible disease that it was. We no longer have dysentery epidemics affecting adults. We still do have dysentery, however, in children. One of the very troublesome things is the prevalence of these mild types of dysentery in mental hospitals. And they have been most difficult to control because of the character of the patients. We also have them in children's institutions. Nevertheless there has been a continual diminution. It is kept alive by carriers, as Professor Shiga has said, and there are many carriers. The carriers persist as carriers for a long period. However, improved personal hygiene and improved sanitary engineering will gradually bring about a different condition.

It is rather curious that in the work of the sanitary engineers so little provision has been made for children, either in luxurious houses or in primitive communities. To a great extent the sanitary engineer has forgotten to provide for the needs of the child. This resulted in the appearance of certain foci of the disease, due to the fact that the children had been overlooked by the sanitary engineers and proper provision had not been made for their convenience.

The present classification is an eminently sound one and no doubt will come into use more and more.

It was interesting to hear Professor Shiga say that the Shiga type of dysentery had almost disappeared from Japan. Of course, it has almost disappeared from the United States. It is rather rare in the north and is not common anywhere. But there are foci of Shiga dysentery scattered here and there throughout the southeast. These have been described by Dr. Holt, of Charleston, South Carolina, and the epidemiology of dysentery has been described by Bojlen, of Copenhagen.

Bojlen had the benefit of an extremely well organized public health service, and he was able to follow dysentery epidemics in villages and schools and even in farmhouses. As a result of his study he found many variations in the organisms, which proved to be an advantage rather than a disadvantage. In a particular village epidemic he found the type of organism to be pretty much the same. In another village it will be another type. In a mental hospital certain wards have a characteristic organism which will not be common to the whole institution. He found that in institutions where children and adults were brought, new varieties of organisms are observed from time to time, and that it is possible to have a superinfection, so that a patient will be excreting not one variety but two varieties of organisms.

He found that the epidemiology as a study was facilitated by the variety of characters which the dysentery organisms had, and in time they changed from one to the other.

The preventive vaccination that Professor Shiga spoke of shows that his experience has not been unlike our own in this country.

Vaccination against dysentery bacilli has not been a popular measure, because the reactions were severe. That brings one to a realization of the fact that in enteric diseases, vaccination, while good in emergencies, is not the logical way to prevent enteric diseases. The logical way of preventing enteric diseases is by sanitation and not by vaccination. Vaccination is good for emergencies. So that we can look forward to an improvement in the situation in regard to dysentery as we improve our sanitation and as we improve our personal hygiene.

Professor Shiga remarked that after working all these years of his life on dysentery the end was not in sight. While we may not have seen complete disappearance, there has been a tremendous dimiution in the number of deaths and the number of cases during Professor Shiga's lifetime. I think he is to be congratulated on the permanence of the work which he has done and on its influence throughout the world in the prevention of this disease among adults and children, in a most effective and continuing way. While the work is not entirely completed, it is well launched. We are better off each year and we know in general what to do.

I think we all appreciate Dr. Shiga's effort in coming here and presenting this paper.

COLONEL JAMES SIMMONS, U. S. Army Medical Corps: In this period of world unrest and international bickering it is refreshing to hear the story of a famous scientist who has devoted his life so successfully to the service of mankind. Like many other great men, Dr. Shiga started his life's work with a vision. His dream of eradicating dysentery has not been realized, but, unlike most dreamers, he has lived to see his labors rewarded by an appreciable improvement in world health and by the saving of innumerable lives.

The discovery of the Shiga bacillus in 1898 and the subsequent recognition of related species by others, led to a clearer differentiation of the bacillary and the protozoan dysentery. Subsequent studies of the dysentery bacilli and the methods of their transmission indicated that these infections might be prevented by sanitary methods similar to those used for the prevention of typhoid. Dr. Shiga's introduction of a serum for the treatment of dysentery

and his study and experimental work have led to the intensive use of such treatment throughout the world. While little is known as to the effectiveness of serum treatment in infections due to the Schmidt bacillus and while opinion is divided as to its effectiveness in certain other dysenteries, there seems to be no serious doubt as to the effectiveness of antitoxin serums when used in the Shiga infection.

Preventive vaccination against dysentery was first presented by Dr. Shiga, and within a short time its possibilities were suggested by the experiments of Gale. Subsequent workers have produced a variety of vaccines, many of which have been treated with antitoxic serum or with various chemicals, in an attempt to neutralize the Shiga toxin. As General Russell has just stated, the reports concerning the effectiveness of these vaccines, from all over the world, are not entirely convincing. There is, however, sufficient indication to justify their continued study and use.

To those of us who are connected with the medical department of the Army, the prevention of dysentery is of special interest. The enteric group of diseases has always been notorious as a major plague with troops under field conditions. Undoubtedly dysentery has influenced the outcome of many of the decisive campaigns of the world. The records of the United States Army indicate that during the past hundred years there has been a downward trend in the incidence of these diseases except in periods of war or mobilization. The decrease has been more pronounced during the present century. During the Civil War, in a force estimated at about two million men, there were thirty-seven thousand deaths from this cause. On the other hand, during our participation in the World War, the incidence of those diseases was lower than at any time in the history of the world. In a force of more than four million men there were reported ninety-two thousand cases of dysentery, diarrhea, and enteritis combined, and out of those only about five thousand were recorded as dysentery, either bacillary or protozoan. The mortality also was low. There were two hundred and sixty-seven deaths attributed to the diarrheal diseases and only sixty-nine to the dysenteries.

As our troops had not been vaccinated against dysentery, this striking reduction must be attributed largely, if not entirely, to military sanitation, although one is tempted to speculate as to whether the use of triple typhoid vaccine might not have assisted in some unrecognized way.

The question as to what might be accomplished by the use of an additional antidysentery vaccine cannot be answered at this time, but it is possible that it might have caused a still further decrease in the dysentery infections. In view of the importance of these diseases and the present uncertainty as to the degree of protection afforded by the available vaccines, this subject deserves further intensive study.

Our knowledge of the bacteriology and particularly the changes in the pathologic structure, which occur during the growth of all organisms of the enteric group, suggest lines of investigation which may lead to the development of more effective vaccines for prevention not only of dysentery but of typhoid and other related diseases.

Again I wish to thank Dr. Shiga for the privilege of listening to his lecture and to express the hope that in the future his dream may continue to come true.

DR. SHIGA: I believe I shall retire next winter, and after I retire from bacteriology I suppose that dysentery will disappear.

[The scientists attending this section then divided into smaller groups and discussed the subjects informally.]

CLINICAL AND IMMUNOLOGIC OBSERVATIONS IN CASES OF PNEUMOCOCCUS TYPE V PNEUMONIA TREATED WITH SPECIFIC ANTIBODY*

BY MAXWELL FINLAND, M.D.,† AND R. CARMICHAEL TILGHMAN, M.D.†

DURING the past winter and spring there was an appreciable increase over preceding years in the number of cases of pneumococcus pneumonia admitted to the Boston City Hospital. With this increase there was encountered an unusually large number of cases of pneumonia due to the Type V pneumococcus. We were fortunate in having available some concentrated antibody for this type during part of this season. Accordingly, a limited number of cases seen early in the disease were treated with specific antibody. This paper concerns the clinical results of this therapy and serologic studies made in the serum recipients. While the number of cases treated with serum was too small to warrant final conclusions as to its efficacy, the uniformly beneficial effects observed following its proper use strongly suggested that we were dealing with a useful and effective specific therapeutic agent.

The Type V pneumococcus, which is probably the same as the so-called Type IIa of Avery,[1] is one of the most important of the newly classified types of pneumococci (Cooper[2]). As a causative agent in the pneumonias of adults it is exceeded in frequency, among these new types, only by the Type VIII (atypical Type III) pneumococcus.[3, 4] It has been identified as the probable inciting agent in certain institutional[5] and familial[6] outbreaks of pneumonia and other respiratory infections, and is rarely found in the nasopharynx of normal individuals not in contact with cases of pneumonia due to this type.[7, 8, 9]

The clinical and bacteriologic features of infections with the Type V pneumococcus, as observed at the Boston City Hospital, have been reported elsewhere.[10] Briefly, this organism, like the Type II pneumococcus with which it is immunologically related, was found to be associated with pneumonia with considerable regularity. The pneumonias due to both these types are characterized by a similar invasiveness, as indicated by an incidence of bacteremia that is higher than in any other of the com-

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The immunologic studies were carried out with the technical assistance of Mildred W. Barnes.

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mon types, a high death rate and a similar age distribution. The pulmonary lesion was "atypical" in a larger percentage of cases of Type V than of Type II pneumonias. Of all the pneumonias, 26 per cent of the Type V cases were "atypical" as compared with 4 per cent of the Type II cases. Among the autopsied cases alone, 48 per cent of the former and 26 per cent of the latter were "atypical" or bronchopneumonias. Purulent complications, diagnosed during life or discovered at autopsy, were more common among the cases of Type V pneumonias.

The antibody response to infections with the Type V pneumococcus unaffected by specific serum has also been reported.[11] Patients with pneumonia due to this type were found to develop homologous type-specific agglutinins and mouse protective antibodies with great regularity and in comparatively high titers at or about the time of recovery by crisis or lysis. Those that died failed to develop such antibodies. The importance, from a therapeutic standpoint, of the immunologic relation between Type II and Type V pneumococci was reemphasized (cf. Cooper[2]).

PATIENTS, MATERIALS AND METHODS

Patients. The following criteria were used in the selection of patients for treatment with specific serum: (1) the patients were over 12 years of age and had clinical evidence of pneumonia, (2) a Type V pneumococcus was identified in the sputum or blood culture and (3) judging from the time of the initial chill or typical pleuritic pain, whichever came first, the patients were acutely ill not more than 96 hours at the time the type was determined. A total of 26 patients received serum, including 2 patients treated at other hospitals, and 1 that received the first injection of serum early in the fifth day (103 hours after the onset). Since November, 1929, when "typing" serum for Type V was first made available here, a total of 197 cases of pneumonia due to this type, in persons over 12 years of age, have been treated at the Boston City Hospital without specific serum. These include, in addition to the 130 cases previously reported,[10] 67 adult cases admitted between June 1, 1935 and July 1, 1936. All but 7 of the latter cases were treated during the period of this study, but these patients received no serum because none was available, because the disease was of more than 4 days' duration when the type was determined or because the patient already had evidence of recovery by crisis or lysis.

Bacteriologic Methods. Rapid typing from sputum by the Neufeld method[12] was regularly verified by the stained slide microscopic agglutination method of Sabin[13] and by the older standard methods.[14] Pneumococci from the blood, from purulent foci and from various sources at autopsy were isolated and typed. Venous blood was obtained for culture just before the first injection of serum regardless of whether previous cultures had been made. Subsequently, blood cultures were made as indicated.

Serologic Methods. Blood was obtained for serologic studies before the first injection, from 8 to 18 hours (usually on the following morning) after the last injection, usually 1 week later and at other irregular intervals. In patients requiring additional courses of treatment, further blood samples were obtained before and on the morning after such treatment. Tests for type-specific agglutinins and mouse protective antibodies were carried out as in previous studies,[15] the same strain of Type V pneumococcus being used. This strain was maintained at maximum virulence by daily mouse passage. In addition, microscopic agglutinations[13] were done where a rapid qualitative result was desired and with all bloods that were obtained after specific therapy and had failed to show floccular agglutination macroscopically. Freshly grown 8 to 12 hour rabbit's blood broth cultures were used as antigen for this purpose. Controls were carried out with the same serum, using Type VII and Types I or II pneumococci.

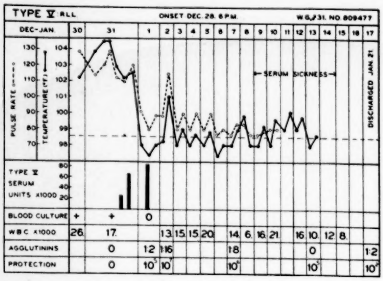
Therapeutic Serum. This was prepared from anti-pneumococcus horse serum and was concentrated and supplied by the Lederle Laboratories, Inc. It was furnished in the form of a bivalent Types V and VII antibody, different lots varying in potency from 2500 to 5000 units of the Type V antibody per cubic centimeter. These preparations were titrated by a method similar to the one now in use for Types I and II antibody,[16] the unit of Type V antibody being taken as equivalent to that contained in 1/150 cubic centimeter of a standard serum (L-1).

The customary precautions were observed before serum was given, including both the cutaneous and conjunctival tests with a 1:10 dilution of horse serum. The initial injection was usually 10,000 or 20,000 units followed, at intervals of 2 hours, by 20,000 to 100,000 unit injections until the desired total was completed. The total dose was chosen arbitrarily and was sometimes curtailed because of the limited supply available. In general, it was planned to give about 80,000 units in each case and an additional 60,000 to 100,000 units if it was ascertained that the blood culture was positive, the amount depending on the effect of the previous dose. In patients under 30 years of age smaller amounts were often used and found to be sufficient. Further amounts were given, when available, if the clinical response was not satisfactory. In 2 patients (cases 6 and 11) serum treatment was interrupted during the first injection because of severe allergic reactions and was not resumed. All of the serum was given intravenously.

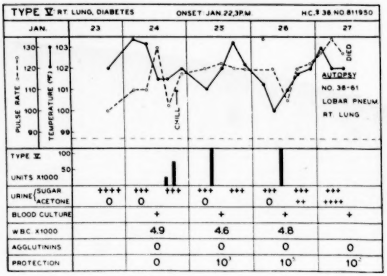
CLINICAL RESULTS

Some of the more important features of each of the serum treated cases are noted in the accompanying charts. In general, the changes observed in these patients after serum treatment were very similar to the effects following the use of specific antibody in patients with Type I pneumococcus pneumonia.[17]

Duration of the Acute Illness. The average duration of the acute illness when treatment was begun was 65 hours. Among the 19 patients that recovered without purulent complications only 4 had fever for more than 18 hours after treatment with serum was begun. The average duration of fever, elevated pulse rate and symptoms of acute illness after the first injection of serum, exclusive of serum sickness, was less than 20 hours. Only 8 of 39 similar cases treated without serum during this time became afebrile and free of the same symptoms within 24 hours after admission to the hospital. The average duration of the acute illness after admission to the wards in these 39 cases was approximately 65 hours. All of the patients that recovered after serum treatment were free of the symptoms of acute pneumonia on the sixth day of the disease. Among those that recovered without receiving serum, on the other hand, two-thirds of the patients were acutely ill on the sixth day and one-half of the patients



CASE 1.



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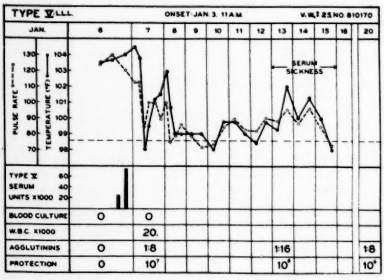

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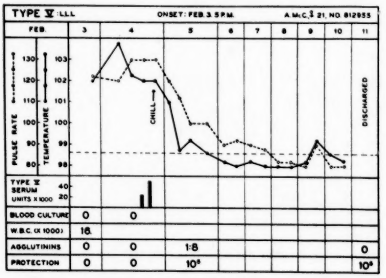

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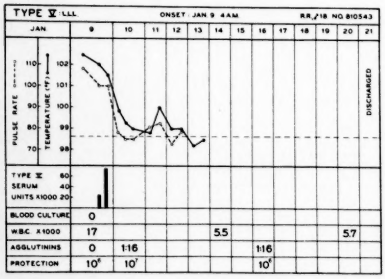

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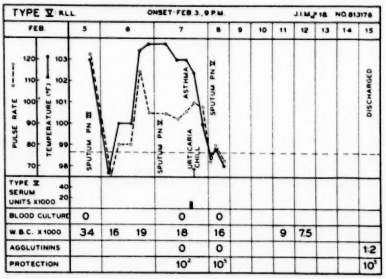


CASE 6.

EXPLANATION OF THE CHARTS

All of the patients had lobar pneumonia. The extent of involvement at the time treatment was begun is noted in the upper left corner. RLL = right lower lobe; RUL = right upper lobe; LLL = left lower lobe, and so forth.

The age of the patient is given in the upper right hand corner between the initials and sex designation and the hospital number.

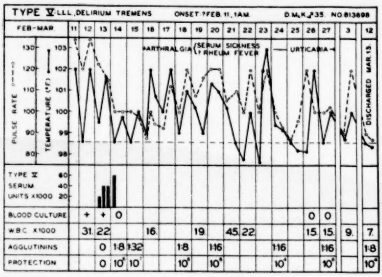
Type V pneumococci were obtained from the sputum, usually on more than one occasion, in every case of Type V pneumonia. These results are not shown in the charts unless especially indicated.

Blood cultures: 0 = sterile; + = positive for Type V pneumococci.

Agglutinins: 1:2, 1:4, and so forth = the highest dilution of serum in which flocculer agglutination of Type V pneumococci was observed. + or ± = moderate or slight clumping of Type V pneumococci seen microscopically in a serum in which macroscopic agglutinins could not be demonstrated.

Protection: 0, 10^2, 10^3, and so forth = the largest number of fatal doses of pneumococci against which mice were protected by 0.2 cc. of serum.

PN = pneumococcus; the type is designated by Roman numerals.



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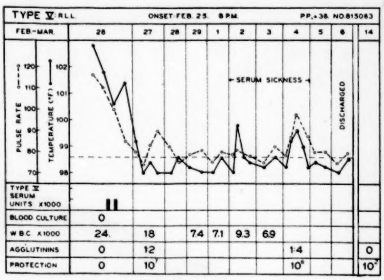
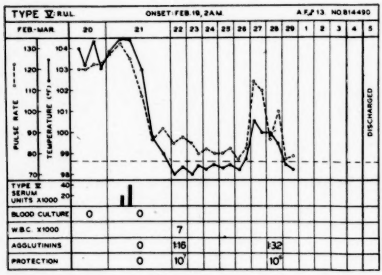


CASE 10.



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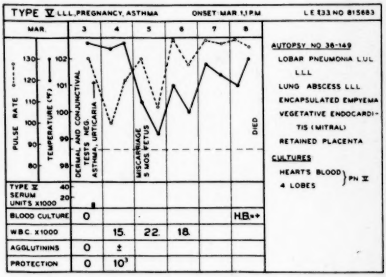

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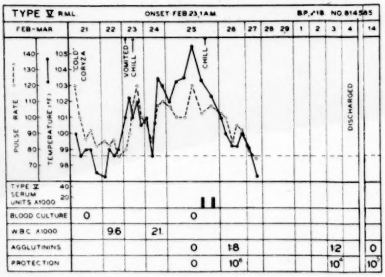

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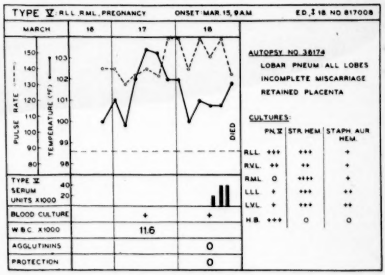

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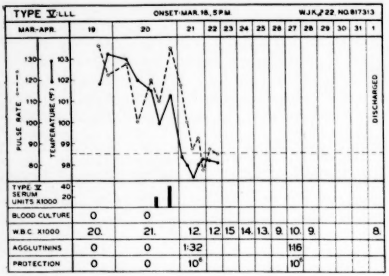

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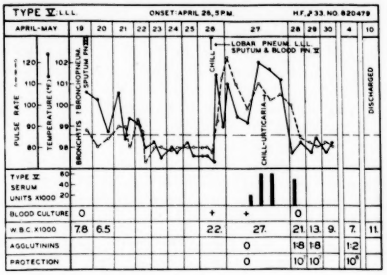

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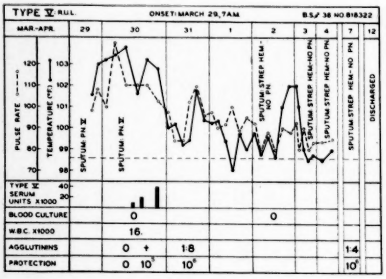

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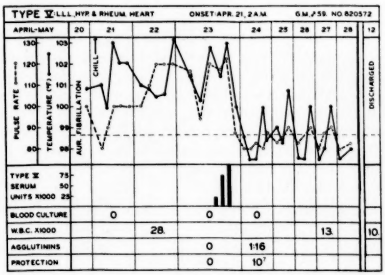

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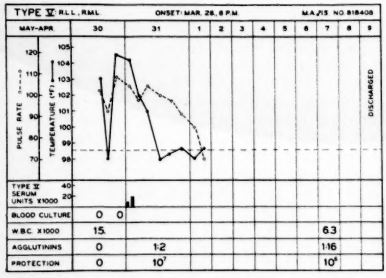

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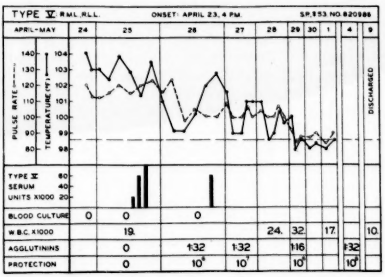


CASE 18.

still had fever and symptoms on the eighth day of the disease.

Bacteremia. Positive blood cultures were obtained before the first injection of serum in 9 cases. In 6 of these cases, all subsequent blood cultures were sterile. One patient, case 20, required a second course of antibody injections before the blood culture became sterile. In case 4 and in case 12 the blood invasion persisted after treatment. Bacteremia was first demonstrated after treatment with a small dose of antibody in case 11. The latter 3 cases will be referred to presently.

Complications. Purulent pneumococcic complications occurred after serum therapy in 5 patients, 4 of whom had positive blood cultures before this treatment was begun. In case 11, an encapsulated empyema and vegetative endocarditis were first found at autopsy. The other 4 patients recovered after operative interference, 2 for empyema (cases 20 and 25), 1 for pelvic abscess (case 26) and 1 for bilateral otitis media (case 22). In case 22, sterile blood cultures were obtained repeatedly. Type V pneumococci were recovered from the purulent exudate in each of these 5 cases. Among the 67 patients treated without serum during 1935-36, 8 had empyema and 6 of these died. In 3 of these fatal cases, other purulent complications were found—pericarditis in 1, peritonitis in a second and meningitis and vegetative endocarditis in the third.

Extensions of the Pulmonary Lesion. These occurred after serum treatment only in case 11. Among the contemporaneous nonserum treated cases, on the other hand, extensions of the pulmonary lesion were shown to occur after admission to the hospital in 13 patients, of whom 5 died.

Fatal Cases. The 4 deaths among the serum treated cases are of especial interest. In case 4, there was severe diabetes mellitus, in which the glycosuria could not be controlled and acidosis developed and progressed in spite of vigorous treatment. Bacteremia, in this case, was not affected but actually increased from 3 to 160 colonies per cubic centimeter of blood, in spite of three daily doses of 100,000 units of antibody. In case 11, the pneumonia occurred as a complication of a septic abortion in a patient with asthma and rheumatic heart disease. Serum was discontinued after only 10,000 units had been injected because of a severe reaction with asthma. The pulmonary lesion extended rapidly thereafter, and bacteremia developed before death. In case 12, an incomplete miscarriage occurred at the end of the third day of the pneumonia. Serum treatment was begun 12 hours later when the patient was *in extremis*. Death occurred within 7 hours after the first injection of serum. The fourth patient, case 19, was a 72 year old colored woman with a positive blood culture when serum treatment was begun. A dose of 68,000 units was given. The patient developed pulmonary edema a few hours later, and, on that account, no further serum was injected when the results of the blood culture were ascertained. A subsequent blood culture was sterile.

Death Rates. The mortality rates in cases treated with serum and in nonserum treated cases are shown in table 1. It is evident from

TABLE 1

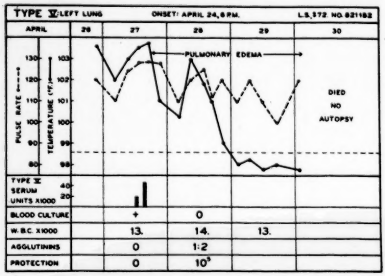
DEATH RATES IN PNEUMOCOCCUS TYPE V PNEUMONIA

	1929-35 No Serum			1935-36 No Serum			1935-36 Serum Treated		
	Number of Cases	Number Died	Per Cent Died	Number of Cases	Number Died	Per Cent Died	Number of Cases	Number Died	Per Cent Died
All Cases	130	64	49	67	26	40	26	4	15
12-29 years	32	8	25	19	2	11	13	1	8
30-49 years	55	25	45	28	8	29	10	2	20
50+ years	43	31	72	20	16	80	3	1	33
Positive Blood Culture	39	34	87	28	21	75	9	3	33
Sterile Blood Culture	61	17	28	36	4	11	17	1	6

the consideration of the fatalities among the serum treated cases and from the experience with other types[18] that mortality figures alone cannot be used as an adequate criterion for the efficacy of any specific treatment. The figures presented, however, are of some interest. The fatalities that occurred before June, 1935, have been analyzed elsewhere.[10] Among the 26 more recent deaths, 6 occurred in patients in whom the pneumonia was secondary to other serious illness. Two began in the course of congestive cardiac failure, 2 complicated the puerperium, 1 followed injuries including a fractured skull and 1 occurred in a patient with carcinoma of the prostate. Four of the 26 deaths, including 3 with secondary pneumonia, occurred within 24 hours after admission to the hospital.

Untoward Reactions. Such were encountered and were similar to those observed following concentrated antibody injections in the treatment of pneumococcus Type I and Type II pneumonia.

Immediate ("allergic" type) reactions were observed in 3 patients. In case 6, "throbbing" sen-



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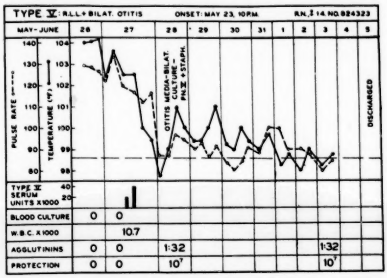

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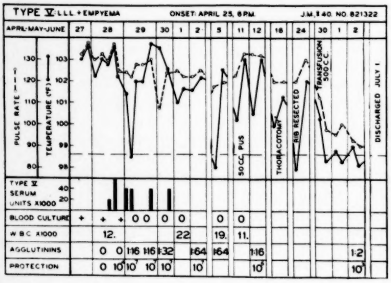

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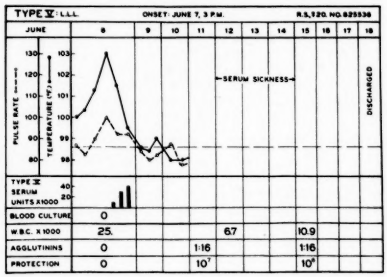

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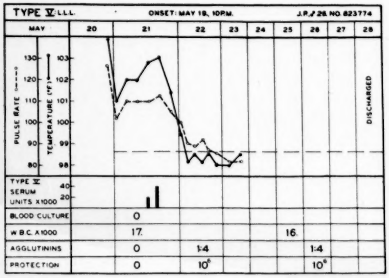
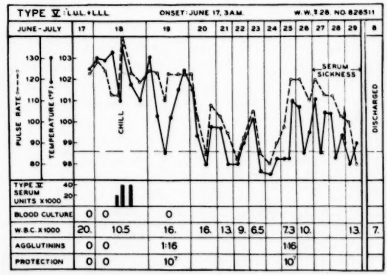


CASE 21.



CASE 24.

sation in the head, flushing of the face, asthmatic wheezing, violent cough, urticaria, vomiting and chill occurred during and immediately after the first injection of antibody, which was interrupted after only 6,000 units had been introduced. There was a history of vaccine injections for "boils" and toxin-antitoxin injections for immunization against diphtheria, but the tests for sensitivity to horse serum were considered negative. This patient was afebrile within 10 hours and no further treatment seemed necessary. In case 11, there was a history of asthma, a negative conjunctival test and only a slight reaction of erythema to the cutaneous test. A severe asthmatic attack began as soon as 10,000 units had been introduced and was controlled only with difficulty. No further antibody was given to this patient. Her pulmonary lesion extended, bacteremia developed, and she died. In case 25, generalized urticaria appeared during the first and third injections of 10,000 and 20,000 units, respectively, and was easily relieved by small subcutaneous doses of adrenalin. A single *chill*, 30 to 90 minutes after injection, was experienced by 6 patients (cases 4, 5, 9, 16, 20 and 24). In five instances this followed the second injection, consisting of 50,000 to 70,000 units, and in the sixth case it followed an initial injection of 20,000 units. The chills were all mild, lasted only a few minutes and were not accompanied by a rise in temperature of more than 2°F. in any instance. *Serum sickness* occurred in 8 patients (cases 1, 2, 7, 10, 23, 24, 25 and 26) and was characterized, in all but one instance, by mild arthralgia and slight fever of short duration. In case 7, the arthralgia began early, recurred, was moderately severe and was accompanied by urticaria in the latter part of its course.

Specificity of the Clinical Response. Four patients with Type V pneumococcus pneumonia have been treated with large doses of Type II antibody. Two of these patients died and the other 2 recovered by crisis 3 and 5 days, respectively, after treatment. No beneficial effect on the course of the disease was observed in any of these patients. The course of the illness in 1 of these patients is represented graphically (case 27). The charts of 3 patients that had pneumonia of other types but received Type V antibody are also shown (cases 28, 29 and 30). No benefit resulted, and antibodies for the patients' types did not appear in the serum after treatment.

IMMUNOLOGIC RESULTS

Mouse protective antibodies for Type V pneumococci could not be demonstrated before treatment was begun except in case 6, in which they were present in low titer. These antibodies were demonstrated, however, in every serum obtained after treatment with specific antibodies, even in patients who subsequently died. In 2 patients (cases 4 and 20) these antibodies were present in the same blood from which pneumococci were cultured, but the titers were lower than those found in other serums.

Type-specific agglutinins could not be demonstrated in any of the patients before antibody therapy was begun. In 4 patients (cases 4, 6, 11 and 20), one or more serums obtained after treatment failed to show Type V agglutinins, although they protected mice against 1000 to 100,000 fatal doses of pneumococci of the same type. In case 12, there was no opportunity to study the patient's serum after treatment. Good agglutination in smears of mixtures examined microscopically was constantly noted with sera in which flocculer agglutinins were demonstrated, even though the titer was low. In occasional serums (cases 11 and 14) slight to moderate clumping was observed microscopically in serums in which no macroscopic agglutinins were demonstrated, but in which low titers of protective antibody were present.

These findings indicate that a balance of Type V antibody can be established and maintained very readily in the blood of patients with Type V pneumococcus pneumonia by the intravenous injection of moderate doses of homologous concentrated antibody early in the course of the disease. In certain patients with bacteremia, however, fairly large doses may be necessary to accomplish this result.

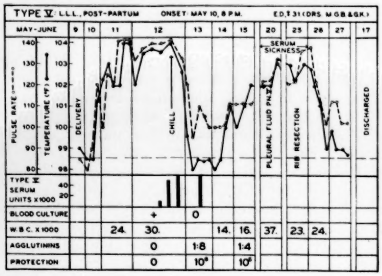
DISCUSSION

Experience with pneumonia due to the Type I pneumococcus[17, 18] has shown that the clinical response to treatment in a succession of individual cases may be a most valuable guide in the evaluation of specific antibody therapy. When a sufficient number of cases are treated with different amounts of antibody, this response may serve to determine the effective dose. Many factors have been found to influence this response, the most important of which are the presence or absence of bacteremia and the duration of illness at the time treatment is begun. Other factors, such as the extent of the pulmonary lesion, beginning purulent complications and other conditions, such as pregnancy and certain preexisting diseases, may also play an important role.

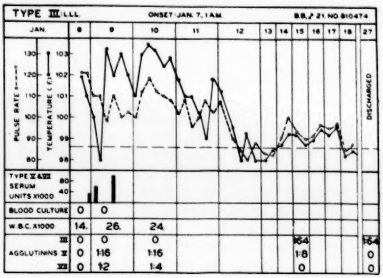
The uniformity with which a condition simulating a spontaneous crisis followed the use of specific antibody in the cases of Type V pneumococcus pneumonia here presented and the fact that the few apparent failures could be reasonably explained suggest that we were dealing with an effective therapeutic agent. Some evidence was also adduced which indicates that the action of this agent is strictly type specific.

The regularity and expediency with which a balance of antibody, similar to and even greater than that encountered after spontaneous recovery from pneumonia due to this type, was established and maintained in the blood of patients treated with serum early in the disease are further evidences for the efficacy of this agent.

The clinical response has been dwelt upon here because the death rates noted in table 1, though they suggest definite benefit, cannot be given too great weight. The number of treated



CASE 25.



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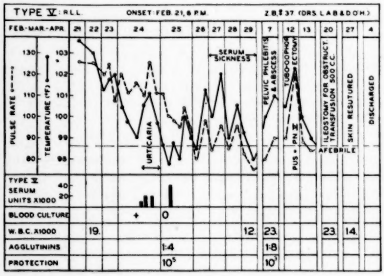

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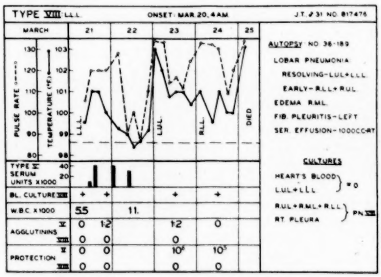

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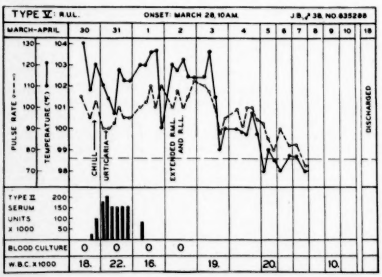

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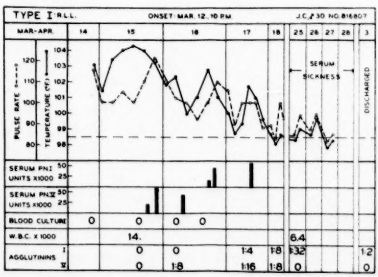

CASE 30.

cases is too small to be significant in this respect, and the age distribution of the cases is seemingly favorable. Bullowa and Wilcox[19] have recently reported their more extensive experience with therapeutic serum for this type. They have used much larger doses and have demonstrated a definite and marked reduction in mortality among specifically treated cases as compared with nonserum treated cases.

No definite conclusions can be drawn with regard to dosage from the limited number of cases available. Certain considerations may be helpful in making a tentative plan of dosage. The increasing mortality of pneumonia in advancing age groups is well known. This has been shown to be closely related to a parallel increase in the incidence of bacteremia with age, except in extreme old age.[10, 18, 20] There is also evidence suggesting that a given amount of antibody may be more effective when given within a few hours than when its administration is spread over more than 24 hours. This is particularly important in bacteremic cases.[18, 21] While it would be desirable, in general, to introduce a huge excess of antibody as soon as possible, a consideration of the limited supply available and of the high cost of producing a potent antibody that gives a minimum of untoward reactions warrants limitation of dosage to amounts not too far in excess of those that may be expected to prove efficacious.

A reasonable, tentative plan of dosage, based on these considerations and the experience in the cases presented, would be an initial dose of 60,000 units in patients under 30 years of age and of 100,000 units in those over 30 and in patients during pregnancy or the puerperium. An additional 60,000 to 100,000 units should be given as soon as it is learned that the blood culture taken before the first injection is positive for Type V pneumococci. The smaller additional doses may be reserved for those that have already shown marked improvement from the previous dose or that show good agglutination of Type V pneumococci in their serums. Additional doses of 40,000 to 100,000 units may be given at 8 to 12 hour intervals for 48 hours, if there is no evidence of marked clinical improvement, unless the persistence of symptoms can be explained on any basis other than Type V pneumococcus pneumonia, such as empyema or mixed infection.

The agglutination test may be useful as a guide before giving additional doses, particularly where fever persists after the other symptoms are definitely improved. If the microscopic test is used, the agglutination must be marked. When bivalent serum is used, it is best to use as controls pneumococci of two other types, one of which corresponds to the other type of antibody contained in the therapeutic serum.

In actual practice the amount of antibody that can be given conveniently with each injection will vary with different lots and will depend on their concentration and capacity to produce chills. In the present cases, 5 patients received 10,000 units and the rest 20,000 or 25,000 units as an initial dose. Excepting the 2 patients that had immediate asthmatic reactions, which were probably associated with specific hypersensitiveness, only 1 patient experienced a chill from the initial dose and this contained 20,000 units. The only other chills encountered followed the second dose and occurred in patients receiving 50,000 units or more at that injection. For these lots, therefore, an initial dose of 20,000 units or less and succeeding doses of 40,000 units at intervals of 2 hours would seem satisfactory. The interval of 2 hours has been chosen because during this interval any chills that may result will have occurred and the succeeding dose may be adjusted accordingly.

SUMMARY AND CONCLUSIONS

The results of early treatment with specific antibody in 26 cases of pneumococcus Type V pneumonia have been presented.

Changes similar to those occurring during spontaneous crisis promptly followed this treatment with fair regularity.

The few poor clinical results occurred in patients that received inadequate doses or that had other serious complicating factors.

The results of tests for homologous type-specific agglutinins and mouse protective antibodies in the serum of these patients showed that a balance of specific antibodies was readily established and maintained in early cases adequately treated.

Some evidence was adduced in support of the strictly type-specific character of the response observed.

The problem of dosage was discussed.

The findings suggest that specific antibody is a useful agent in the treatment of pneumococcus Type V pneumonia, when used in adequate amounts early in the disease.

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ANEURYSM OF AN INTESTINAL BRANCH OF THE SUPERIOR MESENTERIC ARTERY

BY ARTHUR R. KIMPTON, M.D.,* AND SIDNEY C. DALRYMPLE, M.D.*

THE following case is briefly reported as a unique example of an aneurysm of a submucous intestinal artery. No similar case has been found in the literature.

CASE: A 37 year old housewife, past and family history irrelevant, entered the hospital complaining that on the day of entrance she had a sharp, sudden pain in her lower left abdomen which was followed by a loose, tarry movement. Following this movement she fainted. Three weeks prior to the day of entrance she had had severe epigastric pain with nausea and vomiting. This attack of pain was ended by a loose, tarry movement. Upon entrance the physical examination was negative except for a loud blowing systolic murmur, moderate epigastric tenderness and extreme pallor. Her laboratory examinations show occult blood in her stools, an anemia of 1,760,000 red blood cells and hemoglobin of 14 per cent (Sahli).

The patient improved following transfusions. At the end of 3 weeks her stools were negative for occult blood and her blood picture was 3,020,000 red blood cells and 45 per cent hemoglobin.

At this time x-ray studies of her esophagus, stomach, duodenum and colon were negative. However, she was discharged from the hospital with the tentative diagnosis of peptic ulcer and advised to come to the Out-Patient Department for observation.

During the next year her condition remained satisfactory except for occasional nausea, unrelated to meals. Her blood picture remained just below 4,000,000 red blood cells and 70 per cent hemoglobin. At the end of this period she again had lower abdominal pain, usually relieved after passing a soft, black stool.

She entered the hospital again 16 months after the first admission because of pain and weakness. Physical examination was essentially negative, the same as on her previous admission. Her red blood cell count was 2,961,000 and hemoglobin 34 per cent. Bleeding time and coagulation time were normal. Occult blood in her stools was strongly positive at this time.

After five transfusions her general condition was improved. Her blood picture, however, showed but slight improvement. Her stools continued to show blood. A Hinton test on her blood serum was negative.

X-ray studies of esophagus, stomach, duodenum and colon were again negative. The heart and great vessels were normal in size and shape. The mediastinum was not increased in width. The lung fields were clear.

FIG. 1. The vessel at the periphery of the nodule which increased rapidly in size until reaching the dimensions shown in fig. 2.

An exploratory laparotomy was performed 6 weeks after admission, the preoperative diagnosis being "hemorrhage from an adenoma of the small intestine". A very rigid exploration of the entire stomach, small and large bowel at first revealed nothing.

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FIG. 2. The aneurysm of the vessel shown in fig. 1 showing the canalization with fresh thrombus formation and early organization.
The point of rupture through the mucosa is shown with the point of bleeding.

On the third examination of the small intestine, a small nodule, about three-eighths of an inch in diameter, quite solid and hard, was found in the wall of the small intestine, 12 inches below the ligament of Treitz. Upon opening the intestine at this point, a small point in the mucus surface over this nodule was found dropping blood. The nodule was excised and the intestinal wall closed. Following the operation the patient's condition rapidly improved. The stools failed to show any occult blood, and the blood picture rose to 4,750,000 red blood cells and 80 per cent hemoglobin, 5 weeks after the operation. Three months after the operation the red blood count was 4,900,000 and the hemoglobin 94 per cent.

The pathologic examination of the surgical specimen showed a rounded mass, 8 mm. in diameter, partially covered with soft, velvety, pinkish, mucous membrane in the center of which was a slightly raised point 1 mm. in diameter and reddish in color. On section the mass appeared to consist of firm greyish tissue through which passed a few reddish streaks.

Microscopic examination showed an aneurysmal dilatation of a small artery, the wall of which was markedly thickened, partially filled with clot, the periphery of which showed early organization. Several canalized channels led out to the mucus surface through which hemorrhage into the lumen of the intestine was noted. A search at the periphery of the nodule showed the entering vessel, partially thrombosed. The diameter of the undilated portion of the vessel was approximately 0.4 mm. while the dilated portion measured 4 mm.

From a study of this case it is suggested that in operative cases of gastrointestinal hemorrhage without demonstrable ulcerative lesions a careful examination of the entire length of the small intestine be made.

LYMPHATIC METASTASIS IN A CASE OF RECTAL ADENOCARCINOMA SIMULATING A CLINICALLY BENIGN TUMOR

BY WILLIAM M. SHEDDEN, M.D.*

CARCINOMA of the rectum usually metastasizes very slowly and most of the growths with glandular involvement are excavating ulcers showing a tendency to invade the muscularis. In fact, many pathologists state that metastasis does not occur unless the muscularis is invaded. The glands usually involved are those nearest the point of direct extension, and there is apparently no relation between the size of the growth and the extent of regional involvement of the lymph nodes. It has been observed by many that local extension renders a lesion inoperable more often than does metastasis. It is a curious fact that, whereas metastases are commonly met with in the tissues outside the rectum, they are never seen in the wall of the rectum. Miles suggests that the lymphatics of the mucosa therefore probably do not exist as a continuous plexus, but are arranged as decussating arborescents from which collecting stems pass straight through the circular coat to join the intermuscular plexus. Spread, in the latter, is just as limited and so it may be concluded from histologic as well as from clinical findings, that the intramural spread of cancer of the rectum is always of comparatively trivial extent. Occasionally the retrorectal glands are obviously enlarged and can be readily felt, but, in the majority of cases, though the fresh specimen is carefully palpated, it is extremely difficult to be certain whether the glands are enlarged or not.

The papilliferous carcinoma is not particularly malignant and *seldom gives rise to extramural metastases* unless it has been present for a considerable time. A small, soft superficial productive tumor involving only mucosa and submucosa is usually considered benign, and a local excision with a good margin of healthy

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tissue may usually be performed. But a small soft tumor is not always benign and we cannot always be complacent about a tumor of this nature as is shown by the following case history:

J. J. M. (Phillips House No. 24291) entered October 23, 1934 with the story of a slight staining of blood at stool on five occasions during the preceding 2 years, and twice during the past 3 months. He had observed slight constipation and flatulence for 2 months, but had never noticed rectal pain, tenesmus, mucus or weight loss. His past history was irrelevant to the present problem. Physical examination revealed vascular hypertension (180/115), and digital rectal examination demonstrated a polypoid tumor 2 to 3 centimeters long about the same width and at a distance of about 7 centimeters from the anus on the posterior wall. It was not ulcerated, was *soft throughout*, including the base, and apparently was very superficial. Two proctologists had expressed the opinion that this was unquestionably a benign growth and we concurred in this. Biopsy was not done, for it has been our experience that with small rectal growths it is far safer to submit the entire tumor to the pathologist. Four days after entrance, the mass was excised by bipolar electro-

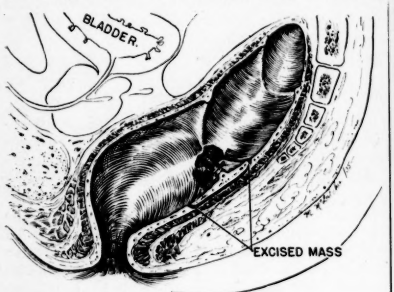

FIG. 1.

desiccation including a margin of about 1½ centimeters of healthy tissue. The operation seemed to confirm the preoperative diagnosis of a benign tumor, for it obviously did not penetrate below the submucosa. We assumed that, barring the presence of other polyps, the patient's rectal troubles were at an end.

But the pathologic report (No. 34-4316) read as follows: A *soft* mass of granular tissue measuring 2 by 1 by 1 centimeters. Diagnosis: Adenocarcinoma—Grade II. (H. F. Hartwell.)

November 13, 1934 a one-stage abdominoperineal resection was performed according to the technic of Miles. The pathologic report is unusual. "At a distance of 7 centimeters from the anus there is a transverse line 2 by 2 centimeters and of purplish-red color. On section there is found beneath this line a narrow zone of bluish discoloration. *No trace of primary tumor can be found*, but there are two small pararectal *nodes containing metastases*."

The patient's convalescence was complicated by pyelitis, but otherwise uneventful. When seen, 24 months later, there was no evidence of recurrence. Here, then, we had a very superficial tumor completely excised from the rectum. That this tumor was, nevertheless, extremely dangerous was demonstrated by histologic examination of the glands draining that organ. A variation of the above case history is one reported by Lockhart-Mummery[8] who excised a soft tumor from the rectum which, on

FIG. 1A. Section from excised tumor clinically benign—actually malignant.

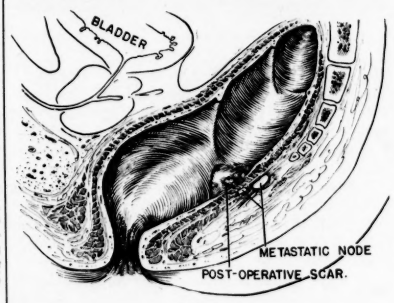

FIG. 2.

histologic examination was found, after several sections had been cut, to be a benign adenoma. When seen 15 months later, the patient had a malignant adenoma in the situation of the previous benign tumor.

Rankin,[8] in a series of cases of cancer of the colon and rectum, found that the incidence of glandular involvement was in direct ratio to the grade of malignancy. Most of the growths in his series were of Grade II and of these 35 per cent had metastases in the glands. Pennington collected data on 997 necropsies of patients dying from cancer of the rectum and in 32 per cent the regional nodes were found to be involved.

C. E. Dukes, in a study of 208 carcinomata of the rectum graded histologically by the technic of Broders, found 125 to be of Grade II. Thirty-six per cent of these had lymphatic involvement. In this group there appeared to be a definite relation between the degree of differentiation of the malignant cells and the extent of spread into the lymphatic drainage.

FIG. 2A. Rectum shows no tumor. Granulation tissue in area of previous tumor.

Oehler[7] reports that 38 per cent of fifty-four patients who died from carcinoma of the rectum and on whom necropsies were performed had glandular involvement in the retroperitoneal lymph nodes.

McVay[4] found metastases in lymph nodes in 47 per cent of one hundred consecutive resected specimens of rectal carcinoma. The high incidence of glandular involvement in McVay's series is probably due to the fact that in his series alone were all the glands systematically examined. Involvement of perirectal nodes does not in itself indicate inoperability, as evidenced by its common occurrence in resected specimens. Early glandular involvement affects so small a part of the gland that it can only be ascertained by microscopic examination. The lymph sinuses at the edge of the gland are first affected.

Miles maintains that the spread of rectal carcinoma takes place earlier and with greater rapidity via the lymphatics than by direct extension. This, of course, is an argument in favor of the radical abdominoperineal operation. His description of the spread of carcinoma of the rectum is now a classic. He emphasizes the fact that there are three lymphatic systems: the *first intramural*, is subdivided into two distinct, freely communicating networks, one in the submucosa and one between the muscular layers, continuous above with the networks of the pelvic colon and below with those of the perianal region and with the inguinal nodes. The intermuscular portion connects with the *second* portion of these lymphatic systems, namely, the *subserous*, lying between the external muscular coat and the perirectal fat. In this second portion of the lymphatic system, a detached cancer cell may wander before entering the *extramural* or *third* portion of the system.

Extramural spread may take place downward, laterally or upward. The downward channel accompanies the inferior hemorrhoidal vessels, and the tissues traversed are those of the ischiorectal fossa, the external sphincter muscles, and the perianal skin. From here the channels empty into the internal iliac nodes. In the lateral extension of the disease, the levator ani muscles and pelvic fascia, coccygeus muscle, pelvic peritoneum, prostate gland or uterine cervix, base of broad ligament, and base of urinary bladder are traversed. Efferent vessels from here reach the uterine iliac group. The paths of the upward main channels of spread accompany the superior hemorrhoidal veins, and traverse the lower mesocolic and retrorectal nodes, the pelvic mesocolon and from thence the nodes that lie at the bifurcation of the left common iliac artery and along the aorta. Miles[5] also emphasized that progress of the carcinomatous cells may be arrested and produce nodules at any point. In estimating the extent of the spread, it is important to know that whenever metastatic growths are visible, distant invisible metastatic growths are likely to be present. Clinical experience in general agrees with this view, and with the method of spread of rectal carcinoma that it suggests. Miles believes it probable that rectal cancer cells become detached from the primary growth almost synchronously with its inception, and finding their way by means of the lymph channels into the surrounding tissues, form more or less distant metastases. It is also probable that detached

cancer cells pass through the bowel wall somewhat rapidly by means of the intramural lymphatic system, and gain access to the external lymphatics giving rise to extramural metastases scattered over a fairly wide area, long before the muscular coat has been penetrated by direct extension of the growth. It is not uncommon to find an involved gland several inches above the rectal growth as the sole evidence of spread along the mesenteric border of the pelvic colon.

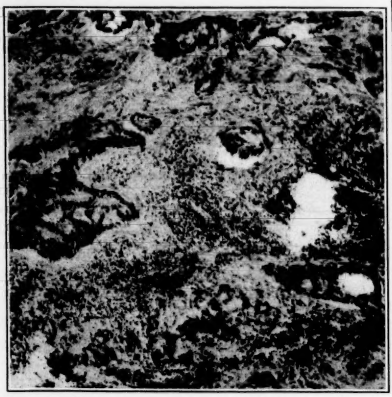

FIG. 2B. Lymph node behind area designated in 1A. Metastatic carcinoma.

It is agreed by most workers in this field that carcinoma of the rectum develops from the crypts of the glands of Lieberkühn which, when they take on their migratory activities, break through the tunica propria of the mucosa into the submucosa, invade the circular muscular coat and, on reaching the intermuscular lymphatic network, tend to progress around the bowel in the direction of these vessels. This accounts for the encircling tendency of rectal carcinoma. From here the cells invade the longitudinal muscle layer and, on reaching the outer muscle wall, their extension is restricted by the rectal fascia. *The invasion of the lymph nodes through the lymphatics may occur at any time after the disease reaches the submucosa,* but such invasion is usually late. Handley has described a marked dissemination in the submucosa occurring early. This he claimed to have demonstrated by mucicarmine staining of entire sections of the bowel. Cole,[2] Monsarrat and Williams,[6] and Cheatle[1] were unable to confirm his findings.

The size of the rectal growth cannot be relied on as an accurate index of the probable lymphatic involvement. Growths without lymphatic involvement tend to grow into the lumen of the bowel. The growths with slight lymphatic involvement tend to spread by direct extension and are slow-growing. Metastatic lymph node involvement can only be definitely determined by systemic microscopic study of all the regional nodes.

SUMMARY AND CONCLUSIONS

We have presented a case history of cancer of the rectum with unusual findings. To depend on the criteria of size, soft consistency and mobility in estimating the malignancy of a rectal tumor is not safe. A "benign polyp" may not only be cancer of a fairly advanced grade but may have actually metastasized when first seen. The above case history serves to emphasize the point made by Miles[5] and others that if a diagnosis of adenocarcinoma of the rectum is confirmed, and if the patient's condition warrants it, nothing less than an excision, having as its upper limit a wide margin of intestine above the growth and including the glands of the mesosigmoid, is justified.

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A WOMEN'S FIELD ARMY

Under the above designation a movement is underway to start a membership drive to enroll at least 50,000 women soldiers in the New York division of the national organization to fight cancer. One of the main purposes of the army is to have organizations in the states throughout the country in order to establish the importance of state activities in the effort to control cancer. Miss Harriet W. Mayer is State Commander of the New York division of the army.

In an address before a conference of the Women's Field Army, Dr. Frank E. Adair, Secretary to the American Society for the Control of Cancer, gave an address which placed the facts relating to the incidence of cancer among women showing that one of every eight women reaching the age of forty years may be expected to die of cancer under existing conditions.

As offsetting these unpleasant facts, he felt hopeful of great progress in the saving of life through education, explaining that under present conditions 25 per cent of women with cancer did the correct thing, as ordered by doctors. Another 25 per cent do not follow doctors' advice. Twenty-five per cent never go to the doctor until it is too late and about 25 per cent are advised wrongly by doctors. These figures show the great importance of an educational campaign by women.

NEW HAMPSHIRE MEDICAL SOCIETY

MORE RATIONAL METHODS IN THE PREVENTION AND CONTROL OF ECLAMPSIA*

BY J. O. ARNOLD, M.D.†

Mr. President, Ladies and Gentlemen:

LET me say to you that I keenly appreciate the opportunity and the privilege of speaking on the subject of puerperal eclampsia. I am keenly appreciative of the responsibility that it involves. Anybody who undertakes to say anything on this disputed question of the etiology and treatment of eclampsia, that is at all different from what is usually accepted, takes double responsibility. If he has something *good*, he has a real responsibility in trying to make it clear so that others may understand it. If it *isn't* anything worthwhile, his responsibility is to get out of the way of the other speakers as quickly as possible.

There are certain applications of general and well-known principles of fluid balance and dehydration upon which we have been working in this field of eclampsia, for a little over six years, and I will pass very rapidly over some of these that, I think, are essential to the understanding of what I shall have to say.

I am speaking as a clinical obstetrician, leaving to the research men of the profession the discovery and discussion of ultimate causes and factors that lie back of the principles that are involved in these newer methods of treatment. We feel perfectly justified in presenting to you these methods as effective measures for controlling the *results* of those ultimate factors or causes, even though we may not yet know all about what those causes are.

For years, it has been assumed by obstetric writers that there could be no rational treatment for eclampsia until the *cause* is known. But we are taking the privilege seriously to question or *deny* this assumption, and to say that we have at least a rational method of controlling the *results* of those causes, and that we believe this to be a forward step of real practical value.

I shall show some charts that I use in my classroom work and present some of the factors vitally involved in the discussion to follow.

The first chart shows the course of normal pregnancy, C-D, with the normal water retention or storage of water in this shaded part, and the normal decrease in output of urine during pregnancy shown in line A. Let us assume that the dotted line B represents the unknown endocrine control factor which is possibly (and we believe, probably), the posterior pituitary body.

Here we have represented the three factors chiefly involved in the very informal talk I shall present on this subject. This first chart

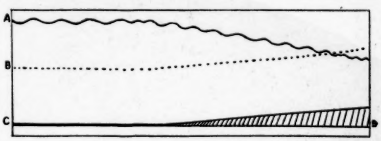

CHART 1.
A. Line of Normal Decrease of Urine Output.
B. Line of Normal Pituitary Increase—Hyperfunction.
C. Line of Normal Weight-Gain—Water Retention.
C D. Course of Pregnancy.

represents the normal, as I have suggested, and I am sure that everything here can be easily verified, and has been many times by ourselves and others; in other words, there is normally a diminution of output of urine as pregnancy advances to term. There is also—at least it has been demonstrated to the satisfaction of ourselves, if not to everybody else—a hyperfunctioning of the pituitary body, as pregnancy advances, as indicated in line B.

As long as these normal conditions are maintained, the so-called toxemia of pregnancy will

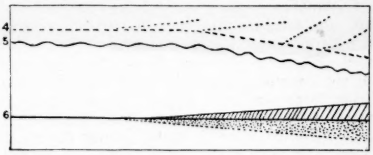

CHART 2.
4. Line of Fluid-Intake—Abnormal Increase—"Pushing Fluids."
5. Line of Normal Decrease of Urine Output.
6. Effect on Weight-Gain, Edema—Potential Danger.

not arise. But, certain things may happen. Certain changes may influence these relations. For instance, the moment we begin to see any considerable diminution in the output of urine, we have been in the habit, many of us, of *increasing* the *intake*, with the purpose of bringing up the *output:* unfortunately, in many instances, this has had the opposite effect. It has resulted in this added shaded line here (chart 2, line 6), which represents the additional storage of wa-

*A stenographic report of an address delivered at the Annual Meeting of the New Hampshire Medical Society at Manchester, May 27, 1936.

†Arnold, J. O.—Professor of Obstetrics, Temple University School of Medicine, Philadelphia, Pa. For record and address of author see "This Week's Issue," page 1250.

ter, with an unnatural weight gain, that can be shown to a greater or lesser degree in any case that develops eclampsia or *near* eclampsia.

I think that we have gone far enough in these six years to maintain beyond contradiction that no woman develops eclampsia or pre-eclampsia, whose fluid-balance, and weight-gain chart, does not show this water-retention. We have demonstrated repeatedly that we do not get the symptoms of toxemia or eclampsia, without it. We go a little farther and say that, so far as we have been able to discover, the only *constant difference* between the normal woman and the eclamptic woman, is this difference between the

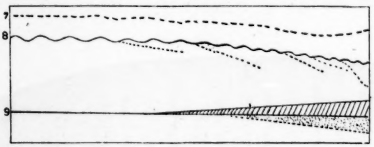

CHART 3.

7. Fluid Intake Unchanged (or Increased).
8. Fluid Output Suddenly or Abnormally Decreased.
9. Abnormal Water-Retention, Weight-Gain, Edema, Danger.

normal and abnormal storage of water. Liver pathology, kidney changes, blood chemistry, blood pressure—none of these are constant—none are found in all cases, but abnormal water-retention *is*.

Maybe I am going a little too far, but the truth of this contention has been so frequently demonstrated to our own satisfaction, on so many of our own cases, that we no longer have any doubt in the matter.

Another way in which this fluid-imbalance may occur, besides increasing the intake, as will readily be suggested, is by a marked diminution in the output, while the intake remains practically the same. For various reasons, the output may be suddenly diminished, such as temperature changes, emotional conditions and various other factors that may occur any time during the pregnancy—and if no corresponding reduction in intake is made, or some other provision for increased output, as by bowel or skin, there surely will be trouble.

Here is a chart (chart 4) of a woman with every condition maintained as in normal pregnancy. She had a fluid-balance, that is, intake and output, amounting to about 45 to 50 ounces at the beginning of pregnancy. After she reached the last five or six weeks, it dropped to an average of 20 to 30. That is typical of many perfectly normal cases that we have followed through.

This chart also illustrates what we call a "trial balance". Not infrequently, or as indicated, a "trial balance" is made, to see if more liquid may be safely taken. This is done by increasing and sometimes doubling the intake for a day or two, and noting the effect on the output. If the kidney response is satisfactory, the larger intake may be continued. If not, it should be reduced to the former amount, or to such daily

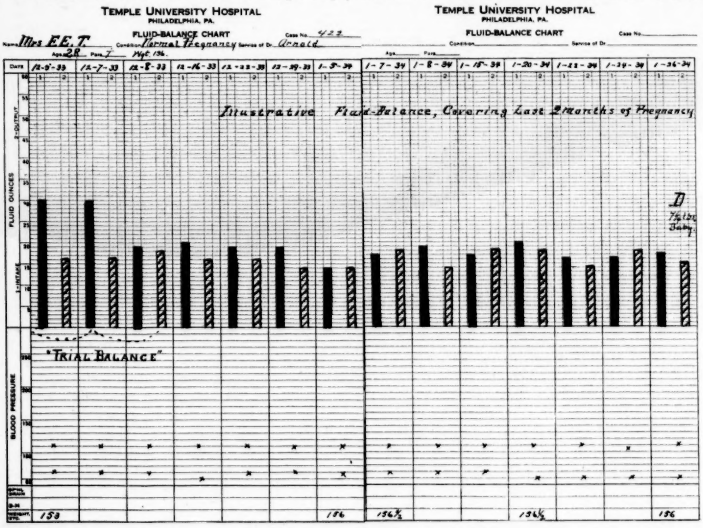

CHART 4.

quantity as will maintain the always safe fluid-balance.

In this particular case, as you see, there was not the response to the trial balance, so we continued to carry this woman on a relatively small quantity of fluid, but with absolute freedom from any symptom or danger sign, and with so

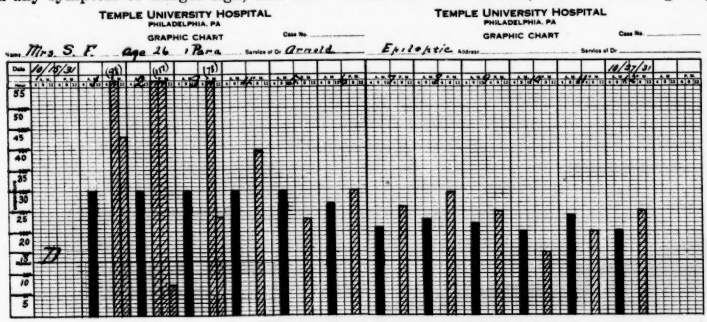

CHART 5.

maternity case (chart 5), that corrects this wrong impression. This young woman in her first pregnancy was put on a strict fluid-balance, as early as the second month, *because* of her epileptiform seizures, of which, by the way, she had none during her entire pregnancy. I cite this case because, for the reason given, we

little weight-gain in the last two months, that in spite of the fact that she was a hale and hearty young woman of good size, weighing 136 pounds at the beginning of pregnancy, she only weighed 156 pounds at the end of pregnancy, and gave birth to a large baby. Of course, you know without my mentioning it, that we estimate

were very careful to keep her down to a fluid-balance of only about 30 ounces a day for many months. She was delivered at term, perfectly normally. She did not show any visible edema. Surely *this* patient has no water storage, but look at her postdelivery output chart. Here are 98 ounces in the first twenty-four hours, nearly

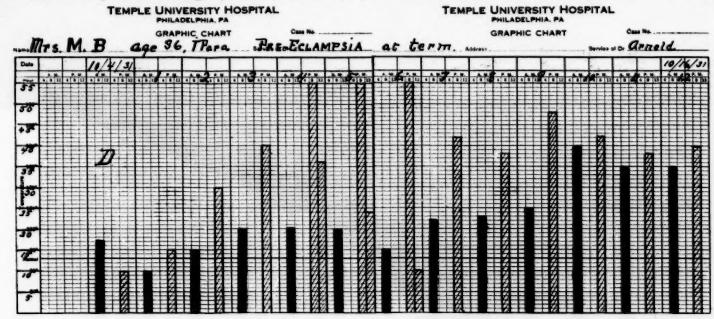
TEMPLE UNIVERSITY HOSPITAL
PHILADELPHIA, PA
GRAPHIC CHART
Mrs. M. B age 36, 1 Para Pre-Eclampsia at term. Service of Dr. Arnold
TEMPLE UNIVERSITY HOSPITAL
PHILADELPHIA, PA
GRAPHIC CHART

CHART 6.

the amount of weight gain by the estimated size of the baby. If we estimate a 7 pound baby, our patient is entitled to twice that weight, or fourteen or fifteen pounds, and so on, according to the size and type of patient.

Now, even though you may have patients who appear to have no edema, and therefore a contradiction to the statement I made a while ago, I want to show you the chart of a woman who happened to be an epileptic, as well as a

as many the next, and so on, for several days, far more output than intake, showing an unbelievable water-retention, even with a very limited intake (indicating on chart).

I want to show you this chart (chart 6) just to show another patient that was bordering dangerously near what we would call an eclamptic or a preeclamptic state, and yet, did not give visible evidence. We thought she was following pretty closely the restrictions on fluids, but we

found out, when she came into the hospital, something quite different. Of course, as you well know, there is an oliguria frequently about the time of labor and immediately after, and that is where we can easily produce our postpartum eclampties, by too rapidly increasing the allowance of fluids, before the oliguria is overcome. Look at the enormous amounts of output here (over 100 ounces a day for a while). This woman did not appear to be edematous, and supposedly had followed closely the restrictions, yet not closely enough, as she afterward admitted. She was spending the summer at the seashore, and her doctor was in Philadelphia. As she intimated, she was literally "between the devil and the deep sea", and as she afterward confessed, she was far from following the fluid-balance instructions given by her doctor. And this chart shows why she came dangerously near eclampsia, though she was professing to follow our treatment.

Here is another interesting case, which I shall bring in at this point, only as a comparison (chart 7).

A short time ago, a patient was brought into the hospital in eclampsia. You will notice that while most cases *gradually* develop their toxemia, this came on rapidly. We had this history from the woman, after her recovery. This was her eighth pregnancy, and about the middle of the seventh month, perhaps, or maybe nearer the eighth month. She had been going along perfectly well, and had not yet engaged a doctor, when a visiting nurse saw her. The nurse measured the urine, as nurses are taught to do, and found that there was an output of less than *three pints* a day, and advised that the patient must drink more water.

It so happened that she was living on the outskirts of Philadelphia. There was a spring nearby. "We have plenty of water; I can easily drink more water," she said. The nurse urged her, therefore, to drink quantities of water. In a week's time, she began to have headache and some edema, and in three weeks' time, we had her in the hospital in convulsions. We did three spinal drainings. Then we began our purgations. The three points in our regular routine are as follows: 1. Spinal tap for immediate relief; 2. hypertonic solutions intravenously; 3. hypertonic solutions by mouth, to dehydrate by the bowel. In so doing, we removed in the first twenty-four hours, after this patient came into the hospital, *142 ounces* of fluid (in the bowel content and in the urine output). We kept her, of course, very much restricted on fluids, and continued to purge her daily for three days, and she rapidly improved.

This woman had no more convulsions. But here (referring to chart 7), on the fourth day,

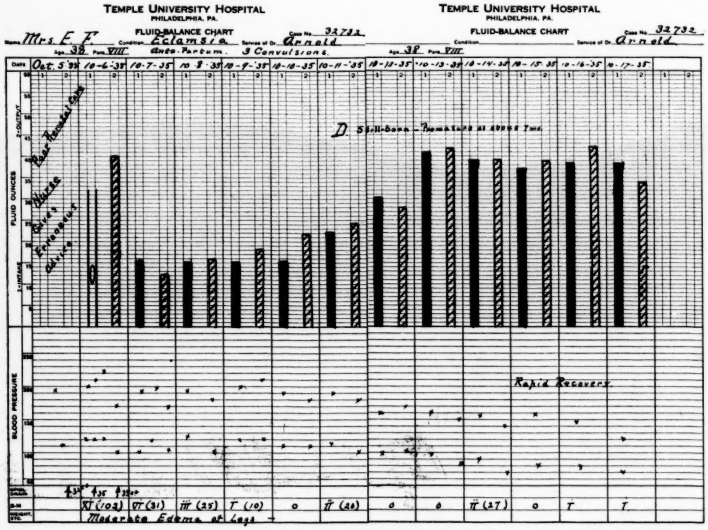

CHART 7.

she was delivered of a stillborn baby. The damage had already been done. Unfortunately, we find that is too often the case, if the woman is allowed to go to such serious conditions, and allowed to have convulsions. Here, then, we had a very intelligent woman, who hadn't a symptom or a sign of trouble until the nurse began to urge upon her the intake of more fluids, to produce a larger output of urine. The unfortunate thing was that when the nurse saw the change taking place, and advised her to go to a physician, the physician, likewise, ordered a purgative or two and said, "You must drink more water and flush out your kidneys. You *must* get them working."

I show this slide (chart No. 8), in order that you may better understand some of the things I am going to say. We have simplified, for practical purposes, the classification of these cases, and have not attempted to base them on the pathology which is still so much in dispute. We place all patients in the following five groups:

CLASSIFICATION OR GROUPING OF PATIENTS

I. The Inherently Normal
Prenatal trouble unlikely.

II. The Potentially Abnormal
Trouble probable, but preventable.

III. The Moderately Preeclamptic
Trouble in moderate degree, now.

IV. The Dangerously Preeclamptic
Alarmingly near the crisis.

V. The Eclamptic or Convulsive Group
Have reached the culminating crisis.

CHART 8.

1. The inherently normal; nothing discovered abnormal at the beginning of pregnancy, or in the history, that would affect the pregnancy.

2. The potentially abnormal. This is a most important group. It seems to me that it is here we need to learn some of our most practical lessons. If we have done anything more important than the actual treatment of these cases, it is in their prevention; it is in emphasizing the great importance of grouping these two classes separately—separating the *potentially dangerous* patients, from the *normal* patients. All those who have a history that might in any way suggest a low reserve kidney, for instance, or previous difficulties in pregnancy, or possible nephritis-producing disease. The moment we get such patients early or late, we put them at once on a fluid-balance, and maintain that throughout the pregnancy, and even though they have diseased kidneys, or impaired kidney function, we do not fear to carry them safely to term, or *near* term, having been forewarned, and having taken the measures to prevent the condition that will bring the trouble.

Let us take the inherently normal patients

I. THE INHERENTLY NORMAL

Normal organic health before pregnancy. Nothing in history predisposing to complications. Nothing discoverable *now* suggesting active or latent disease.

Treatment

Note weight and blood-pressure now—and before pregnancy. Explain prophylactic importance of prenatal care. Correct erroneous notions as to diet, fluids, and kidney function. Point out relation of fluid-balance and weight control. Limit weight gain in 3rd trimester to approximately one pound a week. Expect patient to remain 100 per cent free of "toxemia".

CHART 9.

for a moment. The usual general prenatal care will carry them along, provided we do one or two things to correct the erroneous notions as to the *diet* and *fluids,* and *kidney functions,* which prevail from the erroneous teachings that you and I were largely responsible for in the past. I know that I have done my full share of urging patients to increase fluids, and to cut down on proteid, and a lot of that kind of advice in which we do just the opposite now.

We point out the relation of the fluid-balance, and the weight-control. Our most valuable office equipment now, is not the urinalysis outfit, nor is it the sphygmomanometer. It is the *scales.* The watching of the weight, the rate of weight gain, is of more value, it appears to me, in the light of what we have found in recent years, than anything else. Of course, we have cases where there is undoubted evidence of pathology in the kidneys, to begin with. We may have various types of symptomatology, of high blood pressure, and so forth, and still have a relatively safe patient, *if* we maintain strict fluid balance and weight-gain control.

Therefore, in our own cases, we want to know, if possible, in the beginning, what the weight was before pregnancy, as well as the blood pressure, and to watch the gain in weight, allowing no more than a pound a week in the last trimester; we very frequently allow no gain at all in patients who appear to demand it, and not only that, but, as many of you know, we now have patients in whom we *reduce* the weight right through pregnancy, in spite of their gain. We did this, to the extent of thirty pounds in one patient, with the *best* of results. In this way, we can greatly reduce the size of her baby or prevent its oversize, as I shall perhaps have occasion to refer to later.

With the potentially abnormal (showing next slide), it is a different proposition. These, we

II. THE POTENTIALLY ABNORMAL

"Substandard risks", though apparently well. History of predisposing disease, or previous pregnancy complications. Organically abnormal or questionable before pregnancy. Evidence *now* of active or latent organic disease.

Treatment

Explain possible dangers, and need of unusual care. Start fluid-balance at once—do not wait for indications. Teach patient to make, and be guided by, frequent F-B tests. Watch weight gain, blood pressure, kidney function. Insist on quality of food, not quantity—5 small meals. Meat, milk, eggs, cereals, vegetables, fruits—low in salt and sweets.

CHART 10.

call the "substandard risks" though they appear perfectly well and healthy now, the ordinary tests of the urine, kidney function and so on, revealing little or nothing abnormal.

There is one other point that I wish to suggest here, and that is the matter of eyeground studies, which will reveal that they belong to this class sometimes when nothing else will. In these patients that have any of the history as I have indicated, we watch the weight control and start them at once on fluid balance and carry them safely through.

One of the very best devices for helping this along is to insist on five small meals a day, with a good general variety of diet—meat, milk, eggs, cereal, vegetables and fruits. We do not bother much with the kinds of foods, so long as they are fairly reasonable, but we *do* bother with the amount of fluid intake. The chief restriction is on salt and sweets—these are kept rather low.

Here is a patient (chart 11) who demonstrates what can be done in the way of prevention by this method. This woman came in at the age of thirty-two; it was her fourth pregnancy. She had had two attacks of eclampsia, and lost both babies. Another time, she had aborted and lost that baby. She is the type of patient who, while apparently well, is potentially dangerous.

We carried her through the pregnancy without a symptom, and without ten points variation in her blood pressure, and gave her a normal, healthy child at term. She was sent in for abortion. She had albuminuria and occasional casts, but she wanted a baby, and she was willing to follow instructions, and we were able to carry her through to term, without the slightest difficulty, on strict fluid-balance methods.

This, and other cases like it, had I the time to review them, would at least do something to counteract the statement that has been so largely made that we do wrong in permitting such women to go through pregnancy, because we greatly shorten their lives.

This woman we have watched closely for the past five years, and she is in as good health

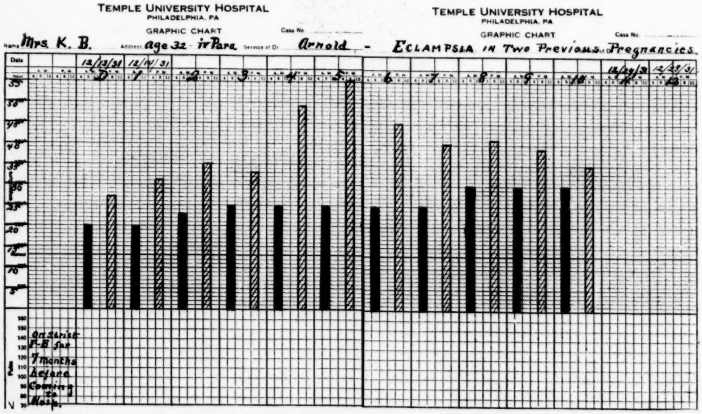

CHART 11.

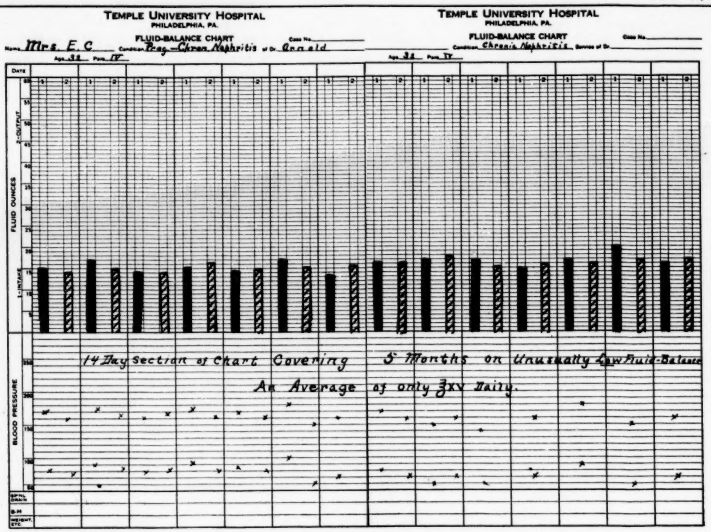

CHART 12.

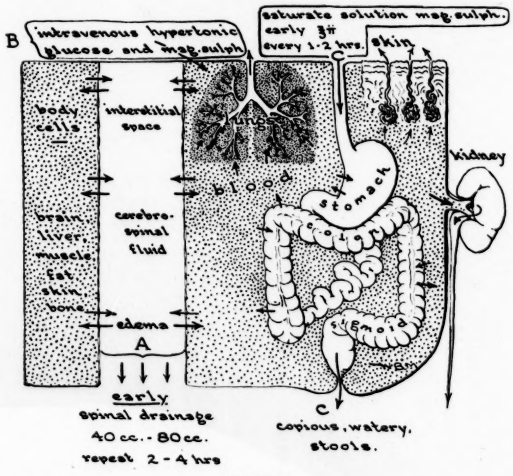

CHART 13.

today as far as anybody can determine, as she was before going through that pregnancy, and I can say in *better* health than she was at the time she came to us. She has a fine, healthy child, and even though her life may be shortened a few years—although there is no indication now that it *will* be—she has had the pleasure of at least five years of motherhood, because we found a way to carry her safely through pregnancy, and even if she does not live to old age, she has left another valuable life in her place, which I am quite sure would not have

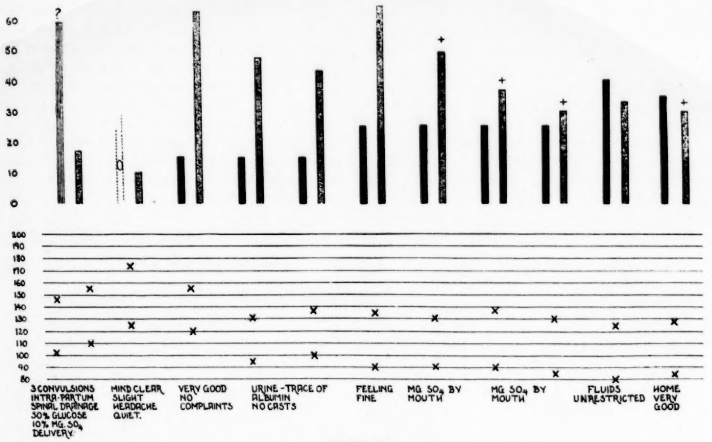
3 CONVULSIONS INTRA-PARTUM SPINAL DRAINAGE 30% GLUCOSE 10% MG. SO4 DELIVERY
MIND CLEAR SLIGHT HEADACHE QUIET.
VERY GOOD NO COMPLAINTS
URINE - TRACE OF ALBUMIN NO CASTS
FEELING FINE
MG. SO4 BY MOUTH
MG. SO4 BY MOUTH
FLUIDS UNRESTRICTED
HOME VERY GOOD

CHART 14.

Mrs. C. H. Age 26. Para I. At term.
Temple University Hospital. Service of Dr. J. O. Arnold.

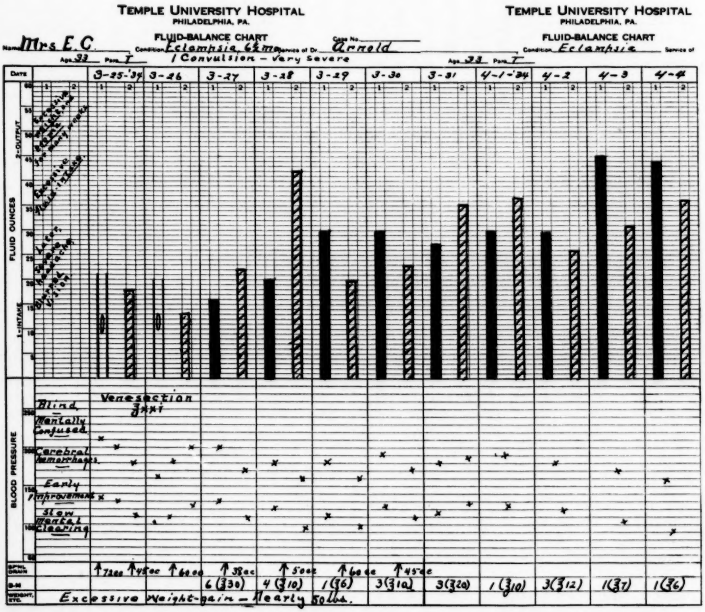

CHART 15.

been the case had we aborted her, and *maybe* the added joy of *motherhood* for a *few* years, will overbalance longer years *without* motherhood.

The next chart (chart 12) is that of a poor woman from the dispensary, on a five months' fluid restriction, and a most remarkable case. We kept this woman on an average of fifteen ounces, fluid-balance, for five months, and gave her a living child, whereas she had lost the fetus in three previous consecutive pregnancies. She has chronic nephritis, and chronic hypertension, from which she suffers as soon as she becomes pregnant. We do not expect to affect that materially, but we *do* know that in following up this case, if we increased or doubled her fluid allowance, this woman's symptoms would immediately begin to return; in fact, on at least four occasions in the nine months, we had to bring her into the hospital, and reinstruct her on keeping a balance. She was of the type *mentally*, to make her one of our most difficult cases, and yet, we demonstrated that by fluid-control alone, such a case *could* be carried through safely.

So much to indicate what can be done with a class of patients usually considered impossible in the prevention of eclampsia.

I should like to show you, at this time, one of Dr. Fay's diagrams (chart 13). I must take this opportunity to say that I owe my interest in this work, to Dr. Temple Fay. It took about a year and a half of persuasion and coaxing on the part of Dr. Fay to get me to try out dehydration in eclampsia. I felt pretty well satisfied with our results, and with our mortality, by the old conservative methods (more than four times as high as we now have), and it was hard to feel that a change might be advantageous,

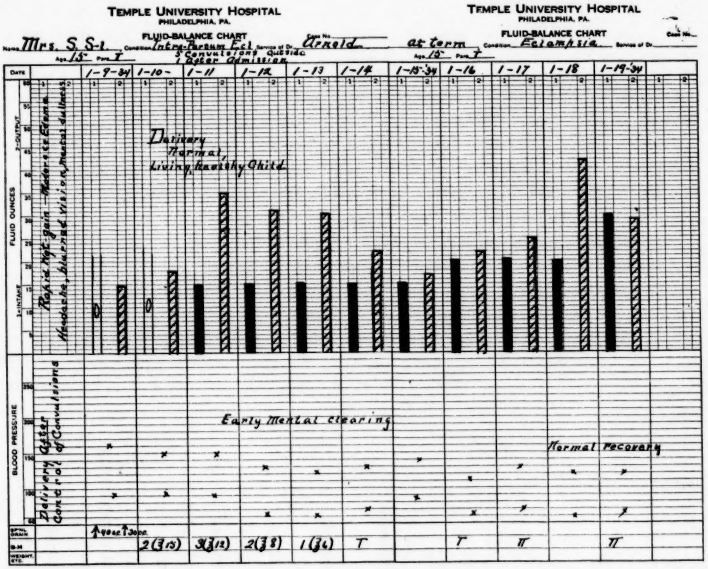

CHART 16.

but Dr. Fay kept after me until I finally did try it, and I have felt very grateful to him ever since.

A glance at this diagram will, I think, give you an idea of the principles on which we base the mechanics of this work. Let this represent the three compartments of the human body, in which the water is contained. We are not particularly concerned with the water-content of the body cells, or with that in the bloodstream, which is more or less unchangeable except very momentarily, but we *are* concerned with the water-content of the cerebrospinal system and that stored in the interstitial spaces of the body; in other words, the *excess* of water, producing edema and intracranial pressure, disturbing the cerebral functions and resulting in the

various manifestations seen in eclampsia, or in conditions leading up to eclampsia.

Here is what we do: We temporarily drain this fluid (indicating on chart) by spinal tapping, making from one to six or seven drainages, as the necessities of the case may indicate. This is done, as a temporary relief, usually, while we are waiting for the other and more permanent dehydrating methods to work. Hypertonic intravenous solutions carry the water over into the bloodstream, which, of course, is only of momentary benefit, unless an early avenue of escape for this blood-borne water is provided through the bowel. We usually ignore for the time, the kidney action. We do not bother giving diuretics, for relief must come *earlier* than the kidneys can provide it.

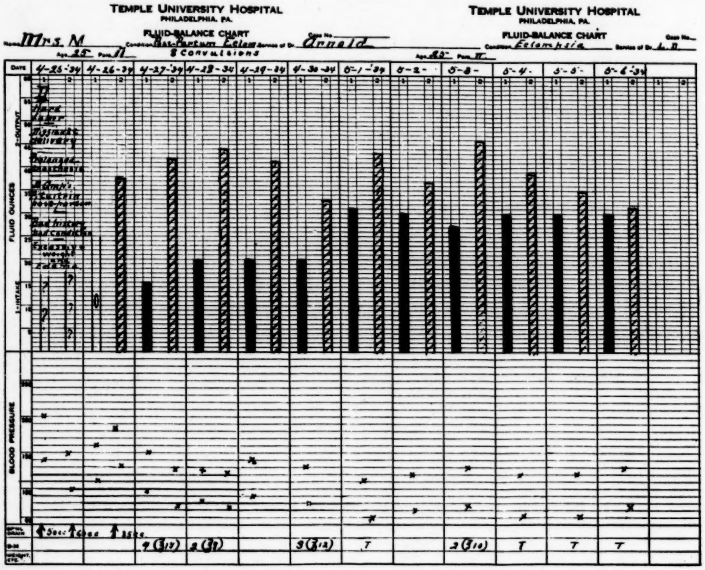

CHART 17.

The moment we begin to do spinal drainage, we begin to give intravenous solutions. Then we start, likewise as early as possible, to give a saturated solution of Epsom salts by *mouth*, to get drainage started from the bloodstream through the bowels. *It is just as important to get the water out through the bowels, as to get it into the blood.* That is one of the points on which I find a good many have failed. They have reckoned on the glucose and magnesium sulfate as therapeutic agents in themselves, instead of merely dehydrating agents, attracting water into the blood, but they have not provided for the satisfactory outlet for that water through the bowels. It is just as important to use some method for getting water *out* of the blood system, for example through the gastrointestinal tract, as it is to get it *into* that system.

We have seen case after case in which the output of urine was so extremely small that we have been implored by our friends, especially on the medical side, to use these newer diuretics, but we have maintained that the kidney is not to blame, and that if we succeed in getting dehydration early enough, the kidney action will return to what it is capable of doing, depending, of course, on whether it was a *normal* kidney to begin with.

Also, note this point. We give 50 cc. of 50 per cent glucose, alternating in two hours with 20 cc. of 10 per cent magnesium sulfate for about three or four doses. We do not give magnesium sulfate long, not more than three or four doses intravenously any more, and the saturate solution by mouth as often as will be necessary to secure watery purgation. I should like to speak longer on this, but I know I must hurry.

My next chart (chart 14) is one of our first cases of eclampsia to be treated after this method was put into force. I show this chart chiefly be-

cause it has a point or two that I should like you to understand. This woman came as near demonstrating the results of experimental forcing of fluids as we could get anywhere. She was a young woman of twenty-six, in her first pregnancy, and absolutely free of symptomatology as late as the beginning of labor, when I saw her and went carefully over her case. There was not a sign of edema and not a complaint, except of the labor. She had a breech presentation, and the interne asked me to see her to verify his diagnosis of breech, and to give a prognosis as to the labor. That was at ten o'clock in the morning, and at two o'clock, he called, stating that the patient we had seen so normal in the morning, was having the most furious convulsions. The orders were as follows: "That is the patient we have been waiting for, for nearly a year. Give no sedatives, give intravenous solutions, and get ready for spinal tap." By the time I got to the hospital, he had already made the drainage, and the patient had, in less than an hour after the spinal tap, regained consciousness, was perfectly clear and rational, and was going on with her labor. In three hours, we did another spinal drainage and found by that time that dilation was complete and labor had progressed to the extent that we felt it would be wise to complete the delivery. After the second tap, with the needle in place, spinal anesthesia was given, and we delivered the woman perfectly painlessly under spinal anesthesia. She tells us to this day what a wonderful delivery it was, because she could lie there and know all about it, even hearing the baby cry, and felt no pain.

Referring again to this chart, the point I want to make is that this large line (indicating), represents an *indefinite intake*. This was a hot July day, and she said that she drank "gallons of water" at home, and when she came into the hospital, the nurse placed a pitcher of ice water on the table alongside of her bed and she continued to drink *ad libitum*. So, in twelve to fourteen hours, she literally drank herself into convulsions. She had stored a large quantity of fluid against an output which had dropped down to a very few ounces. The attack was of very short duration, for we knew the cause, and began effective dehydration at once. There was no time for the development of pathology here, and we found none. She returned to normal consciousness very quickly and made a very good recovery, with no evidence, in the urinalysis, of any kidney involvement. She had only been a few hours under the destructive influence of this condition. We knew that by removing the water and giving her none for twenty-four hours, that we would undoubtedly take away the cause of her convulsions.

I do not believe this was a mere coincidence. I do not believe that we "diluted the toxemia" in this woman's blood and therefore relieved her, by giving more fluid; I do not believe that she would have made such a rapid recovery under any other method of treatment that we might have instituted at that time, because we have had occasion many times since then to verify such methods, and to repeat the results in similar cases. None, perhaps, was ever quite so strikingly instructive as this one.

Let us contrast this case with a primipara 33 years old, who had reached six and a half months (chart 15). There is a whole story in this case that I haven't the time to dwell upon. She was blind, and mentally confused. She had one convulsion at the time she reached the hospital. She was excessively edematous. She was a typical case of one who had been neglected and allowed to accumulate a large excess of fluid in the body,—probably nearly 50 pounds weight-gain. She was one of the worst cases we had, although she had only one convulsion.

For forty-eight hours we gave her no fluids. We found there were but twelve ounces of urine in 24 hours. We did a spinal tap of 72 cc., and four hours later, 45 cc., the next morning 60 cc., and we continued to do daily a drainage of 45 to 60 cc. until this woman had completely cleared mentally—seven drainings in all.

I am frequently asked, "How long do you drain, how much, and how often?" If one draining gives relief, that is often enough, but as in the patient whose chart I have just shown to you, many more are sometimes necessary.

In this last case, we found there were undoubtedly cerebral hemorrhages, so we continued to drain until the spinal fluid became clear. She was several weeks recovering her eyesight, whereas the other woman recovered in a few hours. But this woman had been months on fluid imbalance, which could easily have been prevented, I am persuaded, as in hundreds of other cases, if, at the beginning of edema and rapid weight gain, there had been restriction of fluid, a fluid-balance established, and in addition, dehydration to the extent necessary to keep the weight down. She made a complete recovery. I have been watching her since from time to time, and I have seen no evidence of any permanent injury from her very severe attack.

Here is a case of a young woman in convulsions (chart 16), who had about five outside, and one after she was admitted to the hospital. We think that we are not doing very well if we permit more than one or two convulsions after the case has been placed under our care. I recall a patient in whom there was considerable disappointment, because she had been in the hospital three hours, and they had

not been able to control the convulsions (chart 17). The assistant staff had done everything as usual, but she was still having an occasional convulsion. I looked up the history of the patient. She had been delivered outside, and given an ampoule of pituitrin as soon as delivered. The doctor said he had a very difficult delivery, and used forceps and a *lot* of anesthesia, as well as pituitrin. An hour later, he thought she was still bleeding a little too much, so he gave her

We have not done a cesarean for eclampsia in the six years that we have practiced these methods. I do not know that we may not, sometime, but if we do, it will probably be because she has another indication for it, in addition to the eclampsia. We used to do it, but we feel now that we can avoid the necessity for it if we properly dehydrate these patients, and we have been able to do so now, in something over 230 cases.

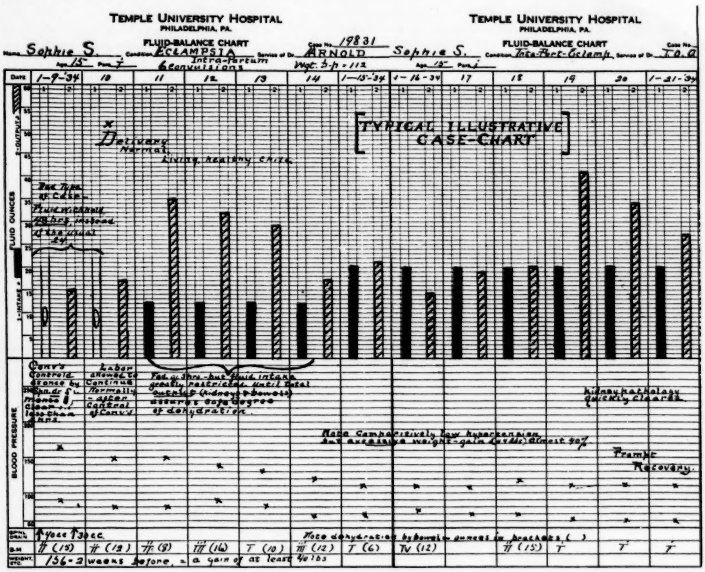

CHART 18.

more pituitrin. If there is anything in the idea—and there does appear to be—that the pituitary body influences water-retention and eclampsia, then it shouldn't be given, and we do not use it in our eclampties or threatened eclamptic cases. We *did* quiet those convulsions, but it took longer because of the pituitrin, probably.

Here is a woman who had severe convulsions (chart 18). We found the output very little, but it began to increase the third day. While the kidney output is low, we always eliminate as much water as we can through the bowels.

We further insist upon this point, that we do not bother with the delivery or terminating the labor, where that is necessary, until we have established a fluid balance and relieved the convulsions. If the uterus is to be emptied, we do it *after* we have controlled the eclampsia. *then* it is safe to do it.

While I do not wish to make a point of our mortality, as that is a subject which none of us dare mention without some humiliation, yet we *can* say this: in the six years, we have had but *six* deaths, only *three* of which could in any way be charged against this method of treatment, and all of these were neglected cases. We have, in our own experience, and in that of many others reporting to us, accomplished two or three things that appear to me to make this method seem at least to *merit* the title of our paper—"More Rational Methods in the Prevention and Control of Eclampsia."

In the first place, we have attained a perfectly serene *attitude of mind* toward these cases that we did not have before, because now we feel very definitely:

(1) *That we know exactly what we want to do.*

(2) *We know equally well why we want to do it.*

(3) We think we know, after these years of experience, *how to do it efficiently,* and so thoroughly that we have reduced our mortality to *less than one-quarter* of what we *thought* was a good maternal mortality, under the old methods.

I feel very seriously about this problem and I hope that even though I have had to hurry very rapidly over a part of this subject, that I have, at least, excited interest enough that you may investigate further and try it out in your practice. If it is all wrong, you, who do the work, will prove it so. If it is *right* (and I am sure you will find it is), you have no right to follow the older and more irrational methods that still largely prevail throughout the country.

I have some booklets that outline this treatment, and if any of you would care to have a copy, I shall be very glad to have you take one.

I want to thank you for your indulgence.

DISCUSSION

PRESIDENT ABBOTT: Discussion on this paper will be opened by Dr. Benjamin P. Burpee of Manchester.

DR. BENJAMIN P. BURPEE: In all medicine there is probably no single condition as yet so obscure both as to etiology and treatment as that of eclampsia. Not more than three or four years ago De Lee made the statement that in two decades not the slightest advance had been made in discovering the cause or in improving the treatment of eclampsia. This is probably much too pessimistic an outlook, because progress is undoubtedly being made. Yet it is a fact that there are a great many different ideas and theories, making the entire subject a very difficult one for the ordinary practitioner to clarify and correlate in his own mind.

For this reason I am sure that I voice the sentiments of all those members of the Society that are interested in the practice of obstetrics, in saying that we are grateful to Dr. Arnold for his paper and for the work that the Temple Clinic has been doing in the last few years along this particular line of theory as to the etiology and treatment of this condition.

The "toxemia" theory, which I believe was first advanced by Bouchard, in 1887, was never very clear cut or definite. The "toxin" was a loose term applied to a certain something circulating in the blood and affecting the various organs of the body producing the symptom complex.

The hypophyseal theory has many advocates. Authors have shown that the administration of hormone substances from the posterior hypophysis will produce in animals a symptom complex like eclampsia even to the pathologic changes—without actual convulsions—also that the hypophyseal substances controlling water exchange and blood pressure are present in increased amounts in the blood of eclamptic women. Yet we have no definite proof that the administration of pituitary in toxemic cases will produce convulsions. Other authors agree that practically all eclamptics will show excessive amounts of prolan in the urine and blood, and that most of them will show a decreased estrin.

Many authorities disagree with the use of the lumbar puncture during convulsions, holding that in these eclamptic cases manometric readings fail to show an increased pressure, and also that in their experience the use of the lumbar puncture has failed to show results. Some pathologists also fail to agree that all eclamptic brains at autopsy show edema.

With such a divergence of opinion as to etiology and treatment, what is the ordinary practitioner to accept? The ordinary run of physicians doing obstetrics must leave to the skilled man with a large amount of material at his command and the facilities for scientific laboratory work, the matter of settling the question of etiology.

For us, who do an average amount of obstetrics, the task is to see to it that each patient receives the best prenatal care possible, adhering strictly to what we call the ordinary standards of prenatal care as a minimum. Frankly there is room for improvement in this State. Our maternal mortality from eclampsia is too high. Ten women out of a total of 45 deaths in this State last year died from eclampsia. Some of these deaths were the fault of the patient. The doctor cannot be held responsible for a death if he does not see the patient until she is in convulsions. However, I firmly believe that the incidence of true eclampsia with convulsions will be small if we all give our patient the best attention that we are capable of, and if—and I believe that this is of extreme importance—we do not hesitate too long in inducing labor on the toxemic patient that is not doing well under medical treatment. Regardless of what the thing may be that is in the maternal system and producing the symptom complex, whether it be a true toxin or a hormone or some indefinite condition, it will not continue to develop after the placenta is detached and I feel that we are violating one of the axioms of medicine when we do not remove the cause. Not so many years ago the teaching was that the uterus must not be emptied until the convulsive condition had been controlled. Now the pendulum is swinging quite a bit toward the immediate emptying of the uterus. Why is it not possible and feasible to treat the condition by whatever appears to be the logical method at the same time inducing labor? In the ordinary patient, and I mean in a multipara with previous normal labors, or in a primipara with the head down and no evidence of disproportion, it is pretty generally accepted that the method of choice in starting labor is by simply rupturing the membranes. If there is fear of disproportion, or of getting into trouble by this procedure, or in early cases to avoid the increased likelihood of intracranial hemorrhage in the fetus if delivered from below as a premature, cesarean section is advisable. The consensus is very much against section in eclamptics. Most authors caution us against doing it. Why? I don't ever remember seeing any reason given why we should not do it. We have been cautioned against many things in obstetrics in the past few decades that are now accepted as quite orthodox procedures. At any rate I would like to make a plea for the earlier intervention in toxemic patients, both in the interest of the patient in preventing continued damage to the various organs, and also in the interest of the fetus, because a baby will not remain alive in the uterus always to term in the presence of a toxemia, and to my mind there are far too many stillborns that might have been saved had labor been induced at an earlier date.

It may be of interest to note that my only experience with manometric readings in eclampsia occurred about two days after the reading of this paper, in a primipara with sudden severe eclampsia and three convulsions. In this one case there was

no increased intracranial pressure. About 2 cc. of spinal fluid was evacuated and the fluid pressure was so low that it would not appear in the manometer.

PRESIDENT ABBOTT: Discussion will be continued by Dr. Robert O. Blood of Concord.

DR. ROBERT O. BLOOD: To follow, on a subject as important as this, men like Dr. Arnold of Temple University and Dr. Burpee of Manchester is a big job. It is such an open question with so much difference of opinion that it is hard to get a large group of us to agree on any one set type of treatment.

It seems to me, however, that Dr. Arnold today has given us a high point to aim at, a lowered maternal death rate which we all desire, and which is quite necessary in every state, and especially in this state perhaps.

Dr. Burpee has told you that one in every four eclamptic women in this state died of this condition.

I believe the greatest thing for us to aim at is not the curing of the disease, eclampsia, but the treatment during pregnancy. It is entirely possible, by the older methods which we have been using, to prevent many cases developing convulsions; it is apparently, from Dr. Arnold's paper, easier now to control this type of disease than it has been in the past.

It was tremendously interesting to me this morning to listen to Dr. Arnold and to hear him tell us that a control of the fluid intake was so important. I think few of us realized that this was important. I have seen my patients gain weight and told them that it was quite natural they should gain weight, without thinking too seriously about the amount of the gain. I think we are all doing this.

We, who practice obstetrics in New Hampshire should consider more seriously all of the preventive methods, and we should consider more seriously our individual qualifications. We should especially consider taking postgraduate work in this field, as we would do if we were practicing surgery or any other field of the profession.

Dr. Arnold has given us a great deal to think about, and I hope that many men in this state will follow his treatment and will get his book and try out this method.

We, of the Committee on Maternity and Infancy, should like to know during the next year how many of you have tried the treatment, what your results are and whether you are satisfied that Dr. Arnold is on the right track.

I wish that Dr. Arnold might tell us in a little more detail how we could use the treatment in the periods before delivery, during the fifth, sixth, seventh and eighth months, and especially whether it is necessary to figure the amount of fluid lost through the dejections as well as the kidney route; also a little more on just how he measures, or rather how he has his patients measure, the amount of fluid intake and output. Those two things, I think, are important.

I think we are all happy to have had Dr. Arnold with us. He has given us a great deal to think about. I should like to hear from him a few minutes along the line of how we shall use the treatment in our daily practice.

I also hope that we shall have the pleasure of hearing from him again at a later date.

PRESIDENT ABBOTT: I shall now call upon Dr. Arnold to close this discussion on this paper.

DR. ARNOLD: *Mr. Chairman*—I appreciate this fine discussion. I should like to answer some of the questions that have been raised by Dr. Burpee, and also some of the other questions.

We use a set of simple blanks like this one which I show you and find it quite easy to teach our patients how to measure the intake and output, and record it on this blank. This plan of having our patients eat five times a day—eating nothing and drinking nothing at any other time—has helped a lot, too. Sometimes, there is a little difficulty to get this going, but once you get the patient started, it is a most helpful device.

We find these methods comparatively easily taught to our private patients. They soon come to understand that all eating and drinking must be done at these definite times—breakfast, midforenoon, lunch, midafternoon and evening—with no big meal at any time. The intake allowance with the five meal plan is easily apportioned—as for instance, 20 ounces a day is six ounces of fluid with each little meal. The patients who are placed on an allowance can be much more easily carried through, if they are on this definite three-hour schedule, with nothing between times.

We have our patients bring their fluid-balance reports to us from time to time, and usually find that they become very much interested in keeping these records.

For instance, a woman of the potentially dangerous type, having had eclampsia twice with the loss of her baby each time, wanted a baby very badly, so we put her on fluid-balance very early. She said she was passing plenty of urine, because she was drinking lots of water. I gave her a chart and explained how to keep it, what she should do, and so forth. When she brought in the first report at the end of a week, we found that the intake was about 75 or 80 ounces, and very much to her surprise, the output was less than half of that, 32 ounces. Now, such an experience is a revelation to a patient, and once we get them to understand it usually, there is not any more trouble, nor was there with this woman throughout the remaining seven months of the pregnancy. She learned how to keep perfectly good and safe, and had no sign of toxemia.

You say the water content of the food must be reckoned with. That is true, but usually, there is also an unmeasurable quantity of elimination of fluid through the skin, so that one more or less balances the other, for all practical purposes.

In the extreme cases, we do restrict them to a more or less dry diet. We do not have the patients live solely on fruits and vegetables, which are almost entirely water. We give them proteins. Take the patient whose chart I showed you, who went through so nicely after three failures. We insisted that she eat meat and proteins and that she keep low on fruits and vegetables. The results were very satisfactory.

I believe you will be surprised to see when you get this information to them so that it is tangible, just how much interest they will take and how they will help you and help themselves.

Now, lest there might be some misinterpretation of this subject, I don't want you to go away from here and say that I maintain this is a cure-all for everything that can happen to a woman in the childbearing period, and that if a woman has a chronic nephritis or any other serious chronic kidney disease, or tuberculosis, or heart disease, and happens to become pregnant, that we are to start in and treat her for the pregnancy and ignore her organic disease. These methods may help her in the course of your treatment for these diseases, but remember that you are treating that cardiac disease or that

kidney disease primarily, and the pregnancy is merely an incident, and its removal early in the pregnancy may be necessary.

I saw such a case with my good friend, Dr. Bland of Jefferson Medical College, only a week ago. This patient appeared to have been perfectly normal before pregnancy from the report given by the family doctor. Very early, at about the fourth or fifth month, she began to have evidence of serious kidney involvement, and soon after that, eye involvement. Undoubtedly, that woman had a serious type of kidney disease and was not a case to be treated purely as a pregnancy. I didn't hesitate a minute to say to my friend, Dr. Bland, that that was a type in which I believed the emptying of the uterus —therapeutic abortion—was absolutely necessary.

When a woman develops eclampsia, or near eclampsia or any of these so-called toxemic signs before the fifth or sixth month, there is more to do than merely apply the principles of water balance. She has organic disease to be treated.

Now, with regard to the mortality or the effects on life from not emptying the uterus early in these organic cases, do not lose sight of the fact that such figures were all compiled under the old methods of treatment. We are accumulating, as fast as we can, from all over the country, data on cases with which to compile a report on our treatment. I am very grateful to those who have reported to us, from here and there throughout the country, their experiences. After a time, we shall accumulate enough for a report. But these mortality rates that our good friends have been giving us are based on methods of treatment that are entirely the opposite, usually, from the dehydration and fluid balance treatment.

While we have had a comparatively limited number of organically diseased, up to this time, that we have carried through, yet, there have been enough to convince us that the results under these methods will have a different mortality rate from the results that were obtained in the older methods.

There are a number of points here, such as that eclampsia does not exist if the placenta has been removed or detached, or when the pregnancy is terminated. I would seriously question that. We have postpartum eclampsia as much as a week and two weeks after delivery. Eclampsia has often been produced postpartum, by pushing fluids before kidney action has become normal.

Someone said to me the other day, "Why may not a woman have eclampsia, regardless of pregnancy?" She may! We had one a few months ago at the hospital, demonstrating that this can be true. This woman had been married seventeen years, and was in her seventeenth pregnancy. In a number of these pregnancies in the past, she gave a history of having had kidney involvement, or toxemia, or something of that kind. Now she gave this definite history: In the three months before this pregnancy had begun, she began to have symptoms of eclampsia. She had two typical *eclamptoid convulsions*, from the description given. And why shouldn't she have? I said to her, "What do you do when you are not having babies?" She said, "I belong to the ward committee of the Women's Political League." "How often do you have meetings?" "We have meetings every night."

Then I questioned her further. "Do you have plenty to eat and drink at these meetings?" "Yes, we always have plenty to drink, and something to eat." "How much or what do you drink?" "I drink beer, or whatever we have, six or eight glasses a night."

So the history was that this woman was loading on large quantities of fluid every night in the week, and her kidneys, through years of injury and repeated pregnancies, one after another, had been crippled. She did not reckon with the fact that they were beginning to put out less and less fluid, and, as she got a little older, this condition was beginning to produce an overhydration which gave her cerebral disturbances, and finally resulted in the convulsions—not typical eclampsia, but typical in the mechanism of their production.

Of course, the moment a pregnancy is added to all this, the condition grows rapidly bad. She had a pressure of 210, and a violent headache, and after seven days, we sent her out of the hospital relieved of this, without a dose of medicine, except to purge her and greatly restrict her fluids. We watched her for a time and then lost track of her.

Again I want to thank you for your much appreciated interest in this subject.

RECENT DEATHS

LUCE—Thomas Warren Luce, M.D., of 82 Court Street, Portsmouth, New Hampshire, died at his home, December 11, 1936.

Dr. Luce was born in Readfield, Maine, February 15, 1870, the son of Daniel and Emily (Ladd) Luce. He was educated at Kents Hill Seminary and took his M.D. degree from the Bowdoin Medical School in 1895. He practiced in Portland, Maine, and East Rochester, New Hampshire, before settling in Portsmouth in 1900.

His memberships included the New Hampshire Medical Society, the American Medical Association, the Rockingham County Medical Society, the American College of Surgeons, the New England Surgical Society and the New York and New England Societies of Railway Surgeons.

Dr. Luce had been president of the State and County Medical Societies. He had many civic associations among which were the following: Vice-President of the New Hampshire National Bank, membership in the New Hampshire Historical Society, the Federal Fire Society, the Masonic Order and the Portsmouth Country Club.

He married Miss Nettie M. Leighton, daughter of the late Adam P. Leighton of Portland, Maine.

Two daughters, Mrs. Isadore L. Smith of Ipswich, Mass., and Mrs. Emily E. Pierce of Long Beach, California, and one sister, Miss Gertrude Luce, survive him.

DUNCAN—Charles Duncan, M.D., of Concord, N. H., died at his home, November 13, 1936.

Dr. Duncan was born in Chelsea, Massachusetts, in 1872, graduated from Dartmouth College in 1898 and from the Harvard Medical School in 1903. He served the State of New Hampshire, first as pathologist and bacteriologist and later as secretary of the Board of Health and the Board of Registration in Medicine. His death ended the longest term of service to the State of any of its officials.

Dr. Duncan was a member of the Dartmouth Alumni Association, the Theta Delta Chi and the Casque and Gauntlet fraternities.

His widow, a son, two daughters, a brother and two sisters survive him.

CASE RECORDS
of the
MASSACHUSETTS GENERAL HOSPITAL

ANTE MORTEM AND POST MORTEM RECORDS AS USED IN WEEKLY CLINICAL-PATHOLOGIC EXERCISES

FOUNDED BY RICHARD C. CABOT, M.D.

TRACY B. MALLORY, M.D., *Editor*

CASE 22521

PRESENTATION OF CASE

A 52 year old Italian laborer was admitted complaining of abdominal pain and distention.

The patient was in good health until about 2 years before entry, when he noticed gradually increasing weakness, loss of appetite, and during the ensuing year a decrease in weight from 165 to 130 pounds. After about 6 months he became dyspneic on moderate exertion and gradually developed edema of the lower extremities. A year ago his abdomen became progressively distended. Despite the accompanying weight increase, however, his arms, chest and face became thinner and the weakness increased. He entered a hospital where he remained for 6 weeks. During this period his abdomen was tapped once and a large amount of fluid removed. Thereafter he felt stronger and was discharged without ascites or edema. He was not able, however, to return to work. Four weeks after leaving the hospital both edema and ascites recurred to a greater extent than previously. Subsequently abdominal paracenteses were performed every 2 or 3 weeks by his physician. During the 5 months preceding his entry to this hospital he vomited about once or twice daily, usually after the ingestion of food. There was no hematemesis. About 4 months ago his vision became slightly blurred and progressed to the point where he was unable to read large print. A month before admission the dyspnea became so marked that talking became difficult. Micturition was scanty and during the 2 days before entry he voided only once and then a very small amount. His bowels were usually constipated but following each paracentesis he had three or four loose stools daily. This ceased as the fluid reaccumulated.

There were no previous illnesses of significance. The patient was accustomed to drink about two or three glasses of whiskey, wine or beer daily.

Physical examination showed a well-developed but thin, slightly dyspneic man with sallow, brownish, dry skin. The sclerae were clear and the mucous membranes slightly pallid. The tongue was dry and atrophic at the tip. The breath was uriniferous. Examination of the fundi demonstrated many small fresh and old hemorrhages with patches of white exudate. Arterioles were narrow and tortuous and the discs pale. Small, firm, shotty nodes were palpable in the axillary, inguinal, and epitrochlear regions. The heart was not enlarged and the sounds were regular. The first sound in the apical region was split, afforded a double impulse, and a systolic murmur was heard in the same area. The neck veins were not distended. The blood pressure was 160/100. The percussion note over both bases posteriorly and the lower portion of both sides of the chest anteriorly was dull to flat. Breath sounds in these regions were diminished to absent and tactile fremitus was markedly decreased. Over the left chest anteriorly between the second and fourth ribs and also between the sixth and seventh ribs a loud, leathery friction rub was audible and palpable in the upright position but disappeared when the patient was recumbent. This rub had both cardiac and respiratory phases. The abdomen was markedly distended, the umbilicus protruded, and a fluid wave was elicited. There were numerous scars of paracenteses below the umbilicus. A firm sausage-shaped mass extended from beneath the left costal border for a distance of 5 fingerbreadths into the epigastrium. No note of its mobility was made and it did not seem to be connected with the spleen. There was generalized abdominal tenderness of slight degree, most marked in the left upper quadrant. Edema was present in the sacral region and in both lower extremities.

The temperature was 98°, the pulse 96. The respirations were 30.

Examination of the urine showed a specific gravity of 1.012 with a large trace of albumin. The sediment contained frequent granular casts, 25 to 50 red blood cells and 4 to 8 white blood cells per high power field. The blood showed a red cell count of 2,300,000, with a hemoglobin of 55 per cent. The white cell count was 12,200, 89 per cent polymorphonuclears. Specimens of stool and vomitus gave negative reactions to the guaiac test. The nonprotein nitrogen of the blood was 120 milligrams. The serum protein was 6 per cent and a van den Bergh showed a normal indirect reaction.

A barium enema passed the ileocecal valve. There was considerable spasm in the sigmoid and in one small area in the transverse colon but no definite organic lesion was demonstrated. A gastrointestinal series did not show evidence of esophageal varices. The stomach was high in position and no peristaltic waves were observed on the lesser curvature throughout the examination. There was also rigidity of the

greater curvature near the lower pole of the stomach. No gross tumor defect was visible.

On the day preceding entry abdominal paracentesis produced 450 cubic centimeters of bloody fluid. Its specific gravity was 1.009 and there were 106 white blood cells per cubic millimeter, of which 85 per cent were polymorphonuclears. Twenty-two hundred cubic centimeters of bloody fluid was removed from the right chest 3 days later. The fluid had a specific gravity of 1.011 and contained 408 white blood cells per cubic millimeter. Of these 60 per cent were polymorphonuclears and no tumor cells were identified. An x-ray of the chest taken after the thoracentesis showed a high diaphragm on the left side. The right leaf was obscured by fluid occupying the lower two-thirds of the right lung field. The heart was transverse in position and there was poor aeration of the left lower lung field. The patient failed rapidly and died on the fourth hospital day.

Notes on the History

Dr. Chester M. Jones: "The patient was in good health until about 2 years before entry, when he noticed gradually increasing weakness, loss of appetite, and during the ensuing year a decrease in weight from 165 to 130 pounds." A very striking loss of weight which must enter into the picture. Of course the most obvious cause of loss of weight of that degree, I should say, was malignancy and we have to consider that from the start.

"After about 6 months he became dyspneic on moderate exertion and gradually developed edema of the lower extremities." The way that is worded makes one wonder whether it may be due to anemia associated with a malignant process or possibly to cardiac failure, but if cardiac failure there has been no preceding story of heart disease. I am inclined to choose anemia as explaining the difficulty in breathing. With the anemia there may have been associated protein lack due to loss of appetite, and a nutritional edema.

Progressive distention of the abdomen has to be due to the formation of ascites, or to a solid mass. Gradual enlargement of the abdomen due to ascites together with gradual wasting which is obvious from the diaphragm up is characteristic of cirrhosis but also may be due to intra-abdominal malignancy with ascites.

"During this period his abdomen was tapped once and a large amount of fluid removed." I am sorry we do not know the character of the fluid obtained at that tap. It might help a little more toward diagnosis. We know, then, that he had ascites and we know there are only a few causes for ascites. Cirrhosis and malignancy are the two most common causes; other possibilities are peritoneal irritation due to tuberculosis, and finally heart disease or Bright's disease. Heart disease and Bright's disease I think can be taken off the list for the moment.

Recurrent ascites in the absence of any more story than we have here could be due to cirrhosis perfectly well, or could be due to malignancy of an unusual type. Here is a story that goes back 2 years. It could be due to an adherent mediastinal pericarditis but that is such an unusual condition that I think it should be mentioned in passing and forgotten.

"During the 5 months preceding his entry to this hospital he vomited about once or twice daily, usually after the ingestion of food." This may have been due to disease of the stomach itself or to the fact that he has an abdomen full of aseitic fluid.

"About 4 months ago his vision became slightly blurred and progressed to the point where he was unable to read large print." I cannot see the significance of that unless we say he has nephritis. I do not think nephritis alone could possibly explain the picture. I suppose it is possible that he may have malignancy with metastases which has involved the eye; but that is guessing too far afield.

"Micturition was scanty and during the 2 days before entry he voided only once and then a very small amount." In other words, he is accumulating fluid in the tissue and the abdomen and possibly in the pleural cavities.

"His bowels were usually constipated but following each paracentesis he had three or four loose stools daily. This ceased as the fluid reaccumulated." I cannot explain that very curious statement. It is true that when you release the pressure in the abdomen by taking out a lot of ascitic fluid that you may get a change in bowel habit and in kidney function. When the fluid reaccumulates and displaces the abdominal contents one may get gastrointestinal disturbances in the nature of vomiting and constipation. The diarrhea may mean very marked edema of the bowel wall due to a protein deficiency. It may mean actual involvement of the small bowel by something like a lymphomatous process.

The dryness of the skin is due to dehydration. The dyspnea may be due to ascites and a high diaphragm or that plus anemia. I am wondering if he is any more brown than the average Italian we see. If there are areas of abnormal pigmentation that is worth considering, because with certain diseases we do get loss of weight, tendency to diarrhea, gastrointestinal disturbances, anemia and some of the symptoms he complains of, but we do not get aseites unless there is some additional complication.

"Arterioles were narrow and tortuous and the discs pale." That suggests that the arteriolar changes may be associated with a vascular neph-

ritis. That will not explain, however, the whole picture.

"Small, firm, shotty nodes were palpable in the axillary, inguinal, and epitrochlear regions." He has shotty nodes which are very small and barely palpable. He was extremely undernourished and any glandular enlargement would be easily palpated. I am inclined to think it is not of any significance.

If his dyspnea is to be explained it is not to be explained on a cardiac basis alone, he may have hypertensive heart disease with associated renal disease, but I do not think his heart is the cause of his trouble.

I do not know what to think about a friction rub with change in position but undoubtedly there is some pleural involvement. It may be due to inflammation or due to metastatic malignant disease. There is no story of chest pain, so presumably it is not due to inflammatory process.

"A firm sausage-shaped mass extended from beneath the left costal border for a distance of 5 fingerbreadths into the epigastrium." Wandering spleens are known to exist and it is possible that this is spleen but the note is made that the examiner thought it was not spleen, so I think we should respect his guess about it for the present at least. It could perfectly well be stomach but that would mean a pretty abnormal thick-walled stomach. I suppose it might have been omentum. He has had a great many abdominal taps and certainly we frequently get a lot of thickening of the omentum and fibrous tissue reaction around it, with fixation of the abdominal wall after many paracenteses which sometimes cause abdominal masses. Yet I cannot feel that the mass has anything to do with the story of frequent paracenteses. I think probably we have something connected with the stomach wall. That is only a guess.

He is tremendously undernourished. Undoubtedly he has edema which may be in part due to renal failure and which may be, to some extent, nutritional. It may be due to massive ascites with some interference with the vena cava.

From the physical examination I do not see how I can make a diagnosis. He has a palpable mass and ascites. He is undernourished, with no mention of a palpable liver and spleen. I do not believe that cirrhosis can be diagnosed from these findings. I suppose that we have to consider malignancy as a possibility. He probably has some renal involvement as well.

The urine has a surprisingly low gravity for a person who was dehydrated. It must mean renal damage. He is not uremic simply because he lost fluid. Certainly one would not have much hesitation in saying that there was nephritis present with that picture. It is not the picture of infection of the kidney so far as I can see. With his hypertension and his age and his negative past history, if we can believe it, I should think it was fair to say he had vascular nephritis.

"The white cell count was 12,200, 89 per cent polymorphonuclears." That could go with infection. Apparently they are normal cells There is no suggestion of leukemia which would interest me as one possibility. I think the slight elevation of white count and definite elevation of polymorphonuclears could go with an irritative process, or with malignancy, or with renal hemorrhage. There is no obvious hemorrhage from the gastrointestinal tract.

The nonprotein nitrogen fits in with a failing renal function, so that our laboratory studies give indication of renal involvement, but nephritis and Bright's disease as such do not give palpable masses in the abdomen unless associated with polycystic kidney. In other words, that type of renal failure as a rule does not cause ascites, and bilateral hydrothorax with recurrent ascites, and the duration would be a very unusual finding simply to be explained on the basis of nephritis alone. The fact that this man has a palpable mass makes the problem just so much more difficult. I am inclined to think the renal involvement is an incident in the disease.

"There was considerable spasm in the sigmoid and in one small area in the transverse colon but no definite organic lesion was demonstrated." That does not help very much and I should like to ask Dr. Hampton whether that might not be true simply from the presence of ascites.

No mention is made of the small bowel here. He has no obvious malignancy of the small or large bowel by x-ray, nor has he any evidence of occult bleeding. Therefore, if he has malignancy it is fair to look elsewhere than the gastrointestinal tract from the pylorus down.

It would be interesting to know whether this mass which was palpated corresponded to the stomach which was seen. I should think the description was consistent with a scirrhous carcinoma of the stomach which does not give gross deformity but involves the stomach wall. It might be the picture of a lymphomatous involvement of the stomach. If he has lymphoma it might cause involvement in other organs as well. I should like to see the plates and have Dr. Hampton comment on them. I think they may be of real importance.

The specific gravity of 1.009 of the abdominal fluid disturbs me a great deal, because it is an unusual thing for us to have a chest fluid or a peritoneal fluid with a gravity as low as that and have blood in it unless this fluid clotted and all we were dealing with was the serum.

A lymphomatous process could give such a fluid with involvement of the peritoneum but

I am surprised that the gravity is so low. There may have been old blood in the abdomen from previous taps or from an irritative process involving the peritoneum and causing bloody fluid.

"Twenty-two hundred cubic centimeters of bloody fluid was removed from the right chest three days later." Again bloody fluid. That is a bit of a coincidence. It is more than a coincidence, I should say; we ought not to get bleeding from the belly and the chest, and it probably means a process involving the pleura and the peritoneum. I do not believe it is infectious in nature. It suggests the possibility of malignancy in some form. I suppose the diaphragm might have been pushed up by ascitic fluid, by a big spleen which was not palpable, or by this mass that went under the ribs and of which we were feeling only the lower portion. Another possibility is collapse of the left lower lobe raising the diaphragm on that side without any connection with the other findings.

"The right leaf was obscured by fluid occupying the lower two-thirds of the right lung field." In other words they had removed two liters but there was still a good deal of fluid there which obscured the picture.

Differential Diagnosis

I cannot give a very air-tight differential diagnosis because it is to me a very difficult case. I can do no more than say I think he has malignancy with involvement of the peritoneal cavity and of the pleural cavity. I do not know whether there is involvement of the kidneys or whether there is Bright's disease as an additional diagnosis, which makes the original diagnosis very much harder to establish. Hypernephroma I suppose is a possibility, with metastases; but these are rather curious metastases for hypernephroma, if I remember correctly, and I am inclined to doubt that possibility. He is said to have a pigmented skin. I suppose hypernephroma or some tumor of that type might give pigmentation. He may be a swarthy Italian and the pigmentation may not mean anything. I do not think he has tuberculosis of the peritoneum or tuberculosis of the pleura with pigmentation or Addison's disease or anything as queer as that. I simply have to say he has malignant disease. I would like to know what Dr. Hampton says about the stomach. I think lymphoma has to be considered very seriously.

X-ray Interpretation

Dr. Aubrey O. Hampton: I would like to agree that he has carcinomatosis but somehow I cannot quite locate it.

Dr. Jones: Dr. Allen has made a good point. No mention is made of rectal examination. There might well have been nodules felt by rectal examination which might help.

Dr. Hampton: In this film taken after the tap you can see that the fluid shadow on the right side did not change much. It is surprising how much fluid you can take out of the chest without changing the x-ray appearance. I wish they could have removed a little more so that I could get a look at the lung root. The lung is collapsed on that side, the lower lobe at least, because the heart shifts toward that side even with the large quantity of fluid. That could be due to fluid accumulating over a long period of time, or disease of the bronchus. I do not know how I could differentiate it without taking the fluid out. The remainder of the lung is clear except for atelectasis. Here is a man with one lung to breathe with, with a high left diaphragm which is not a smooth curve as one would expect from pressure below but there is a rather sharp irregularity.

Barium enema shows spasm in the sigmoid. I do not see the spasm described in the transverse colon but this type of spasm is exactly what we see associated with diverticulitis or extrinsic disease around the sigmoid such as malignancy or infection. It is queer that malignancy produces exactly the same spasm as infection. The cecum is rather small but does not show any filling defect. The ascending colon is rather narrow there. I cannot see enough in the colon to make a diagnosis.

A Physician: If he had intrinsic disease of the colon at this time it ought to be pretty obvious.

Dr. Hampton: The splenic flexure is high. We cannot say he had a large spleen. He may have slight enlargement of the liver. It is not very obvious there. The diaphragm is so high that it might have gone up with it. The x-ray description of the stomach is that of carcinoma of the lesser curvature and here I am trying to prove it is not from these films, because I do not think it is! Certainly the lesser curvature is more irregular and appears stiffer than it should. The mucosal folds are thickened and you can see this shadow that could very well be something infiltrating the wall. They could not compress this fellow because his belly was so big and they could not see much with the fluoroscope because it was so dense, so I realize they did not have much chance. They did not say whether peristalsis was present in the upper portion of the stomach. You would have to say the lesser curvature was diseased either from without or within, either adherent to the liver or due to infiltration. This thing here attracted my attention when I first looked at it, especially since there was a mass there but I think you can explain that defect on the basis of the colon.

DR. JONES: Then you do not think he had cancer of the stomach?

DR. HAMPTON: I think he has carcinomatosis. I do not know where it came from.

DR. JONES: Is there anything in the films to suggest carcinoma of the pancreas?

DR. HAMPTON: I cannot point out the head or tail of the pancreas. It would be a fairly good guess.

CLINICAL DIAGNOSES

Chronic glomerulonephritis.
Uremia.
Carcinomatosis, ? primary (lung, stomach, pancreas).

DR. CHESTER M. JONES'S DIAGNOSES

Carcinomatosis.
Chronic nephritis.

ANATOMIC DIAGNOSES

Cirrhosis of the liver, toxic type.
Subacute glomerulonephritis.
Chronic fibrous peritonitis.
Splenomegaly.
Accessory spleens.
Bilateral hydrothorax.
Arteriosclerosis, slight.

PATHOLOGIC DISCUSSION

DR. TRACY B. MALLORY: I think this is one of those cases that become more difficult the more you find out about the patient. As I was originally told the story in very brief form I guessed the correct diagnosis on the basis of incorrect evidence. I assumed the mass in the left upper quadrant was spleen and on the basis of repeated taps and the large spleen I said he had cirrhosis, and on the basis of the very unusual urinary findings I said he had nephritis. That was correct but the reasoning was wrong, because the mass was not spleen. The mass was an agglomeration of coils of small intestine, the peritoneal surfaces of which were between one and two millimeters thick from dense fibrous overgrowth. The same sort of keloid-like fibrous reaction of the peritoneum was present on the stomach as well and accounted unquestionably for its deformity. The surfaces of the liver and spleen were also involved.

The cirrhosis was a fairly marked and obviously long-standing process. The spleen was a little enlarged but not markedly so, 375 grams, about twice normal. The kidneys were just below normal in size, 270 grams, and showed a slight narrowing of the cortex. Microscopically they showed a very marked subacute glomerulonephritis which I should guess was of no more than six months' duration, just beginning to be chronic.

The case interested me as falling into the category regarding which Dr. Jones's confrères, the gastroenterologists, have written a good deal, the hepatorenal syndrome. The syndrome has never impressed me greatly and I doubt very much if there is such a thing. One does see from time to time cases in which the liver and kidney both show involvement. That is true here but I think you can pretty safely say the liver lesion is years old whereas the kidney lesion is only a few months old. If the two were connected etiologically it would be reasonable to expect processes of approximately the same duration in both places. I think we are dealing here with an incidental nephritis complicating a mild long-standing cirrhosis and I would assume that the peritoneal reaction was due to the repeated tapping. There was nothing to explain why either the pleural or the belly taps were bloody except that they may have scratched a vein in each case.

CASE 22522

PRESENTATION OF CASE

A 63 year old American housewife was admitted complaining of pain in the abdomen.

For about a month prior to entry the patient had vague pain in the left lower portion of the back which became worse when she remained on her feet for any length of time. She ascribed this to an automobile accident which had occurred 2 years previously. On the morning of entry she arose as usual and while cooking breakfast first noted a sharp cramp-like pain in the right lower quadrant. She continued with her cooking, however, and following this ate her usual breakfast. She noted that sitting down relieved her abdominal discomfort but she continued to be up and about during the morning. She was impressed by the fact that sudden standing after being seated caused her pain to become acute. The usual light lunch was eaten and during the afternoon the patient felt well enough to do some ironing. At about 5:00 p. m. a physician was called and he advised hospitalization. The pain had become inconstant during the day but when present had been sharp and boring in character and apparently radiated toward the right hip. Sitting down caused it to lessen and become a sore dull ache. There was no nausea or vomiting and there were two normal bowel movements during the day. This was said not to be remarkable for the patient. There had been urinary frequency every 15 minutes since the onset.

The catamenia had terminated at 40 years but there had been some leukorrhea since that time. For 2 weeks prior to entry vaginal discharge had been somewhat more profuse and malodorous.

Physical examination showed a rather obese elderly woman lying comfortably in bed. The

pupils were equal and active and the mouth and pharynx were not remarkable. The lungs were clear and the heart normal. The blood pressure was 135/80. The abdomen was symmetrically full and there was some tenderness generally although most marked in the right lower quadrant, in which region there was also definite spasm. Pressure in the left lower quadrant directed toward the midline produced pain in the right lower quadrant. No masses could be palpated. Peristaltic movements were active. Vaginal examination showed definite tenderness in the right vault but bimanual palpation was difficult because of lack of cooperation. The fundus was not discerned. The remainder of the examination was negative.

The temperature was 101°, the pulse 100. The respirations were 22.

Examination of the urine was negative. The blood showed a white cell count of 10,200.

Shortly after entry a laparotomy was performed.

Differential Diagnosis

Dr. Richard Dwight: About that pelvic examination, where you cannot feel a fundus it does not necessarily mean, to my way of thinking, that you are utterly vague about the fundus. With a woman of 63 years who has had the menopause twenty years before, the fundus may be very small and atrophied and very difficult to feel even in a well relaxed and not very obese patient, but you can feel around enough to be reasonably sure it is not enlarged. On the other hand, with a very obese and uncooperative patient you may not be able to satisfy yourself whether it is enlarged or not if you do not feel it. In this case I cannot tell what the opinion of the examiner was, but I am going to assume that the fundus was not enlarged.

The presenting symptom in this patient is pain. I do not know what kind of pain the patient was having. You must have some idea what kind of patient is having the pain. That makes it difficult on paper if you have no chance of summing up the patient. This patient was a little paradoxical in behavior. She had pain but it did not bother her enough to prevent her eating breakfast and lunch, and doing housework. Apparently she sat down at intervals for relief. On the other hand, it was severe enough to make her call in a doctor in the afternoon. Another thing is the intelligence of the patient, and the question of how accurately she can describe her pain. Is she a phlegmatic character who will not say she has a pain unless it is real pain, or is she the kind of person who will call momentary discomfort pain? That is difficult to estimate. This patient did her usual work but when she got to the hospital she was either in such severe pain or so apprehensive that she could not be cooperative in her physical examination. We have, then, this patient with slight fever, slight leukocytosis, and the doctor who saw her estimated that her pain was sufficiently severe so that an emergency operation was called for. For that reason I shall assume that she had pretty bad pain in the pelvis, even though she had only a slight white count and fever.

The location of her pain seems to be in the right quadrant. She mentions having had left-sided pain for about a month prior to entry. That pain was vague and bothered her only after moving around and doing a lot of work. I do not believe it has any connection with the present situation. The new pain on the right side was evidently much more severe. She first noticed it as radiating to her right hip and she herself gives us the thigh-psoas test which was not mentioned in the physical examination. She volunteers the information that with her thigh flexed she was more comfortable than when it was extended and also that when she extended her leg suddenly she experienced sharp pain. This would suggest that the pathology, whatever it is, is pretty well out on the right side and fairly well down in the pelvis and that it is motion of the iliopsoas muscle which is causing this discomfort. Another thing about the pain; she classed it as "cramp-like" pain. I think that is a rather difficult word to know the meaning of, but there is no description of it which suggests that it is colicky pain. It does not seem to come and go. As I use the word it is not the same as colicky. The pain is definitely located in the right quadrant both by her symptoms and by physical examination. There is spasm in the lower quadrant, tenderness there, pressure on the left also causes pain on the right, and on pelvic examination there is tenderness on the right side.

We have a patient with this fairly severe pain in the pelvis, slightly elevated temperature, and a white count very slightly elevated. What could cause it? She speaks of having had frequency so we might consider the urinary tract first. The urine is negative. I think that is sufficiently important to rule out the urinary tract in this case. If the pain was due to stones in the ureter we would expect red cells. There is no long history of any urinary trouble, so that I will rule out the urinary tract entirely. Now as to the genital organs, the only thing in the history that refers to them is this question of leukorrhea. I do not think that has anything to do with the case. Leukorrhea in a woman of that age is most likely due to a lacerated and infected cervix. It could be a senile vaginitis or a trichomonas vaginitis. If you assume that the leukorrhea has anything to do with the present illness you have to assume that it is more than something in the cervix,

and that there is a pyometrium. If you are assuming pyometrium and thinking of cancer of the fundus, it does not lead you very far into the right lower quadrant. If there is cancer that is causing leukorrhea I would also expect blood. For that reason I do not think the uterus itself is involved.

The patient fortunately is too old to have a ruptured follicle. She has passed the menopause by twenty years and is too old for an ectopic pregnancy, also too old for acute salpingitis. I think for a woman of that age an infected genital tract would be unusual. People of that age who do contract gonococcus infection have acute vaginitis much the same as children have before puberty. She might have a twisted pedicle cyst but the type of cyst that causes gangrene from twisted pedicle is almost always large enough to be felt. I do not think the very small cysts usually get a twisted pedicle. As there was nothing felt on physical examination, no masses felt either abdominally or by pelvic examination, I am going to rule out twisted pedicle cyst. That leaves us the gastrointestinal tract to consider. It is possible to have a perforated ulcer and practically all the presenting symptoms in the pelvis, also with some urinary symptoms; but if that were the cause I would expect that there would be some past history of indigestion or epigastric pain, with nausea and vomiting, and it would be rather far fetched to suggest that in this case. Coming down lower in the gastrointestinal tract, in fact to the other end, there is a question of diverticulitis. I think it would be quite possible to have a diverticulitis of the sigmoid that would have all this pain located down in the pelvis and, possibly, mainly on the right side, but fairly unlikely to have it on the right side with no tenderness or spasm or pain on the left. There is no history of interference with bowel evacuation and no history of obstruction or diarrhea. Carcinoma of the gastrointestinal tract is something you always have to consider, but again I do not see anything that leads to it.

If she had carcinoma of the cecum which perforated she might have symptoms very much like these in location and character, but you would expect that she might have obstructive symptoms and certainly expect an anemia, and for that reason I am not going to consider carcinoma. There is the possibility of regional ileitis and again I do not think it fits very well into the picture. So what we have left is the appendix. I see nothing in this picture that rules out the appendix, and while I would like to have a little higher white count, at the same time it is possible that she could have acute appendicitis with a white count of 10,000; so I am going to make a diagnosis of acute pelvic appendicitis.

Clinical Discussion

Dr. Ralph Adams: On opening the abdomen through two and a half inches of fat the cecum was found slightly displaced upward with a grossly normal appendix lying free at its base. Against the anterior abdominal wall in the right lower quadrant over the area of most marked spasm preoperatively, one lobule of a large cystic structure was found. This lobule was somewhat blue in appearance. Beneath that the main cystic mass lay. It was about 8 centimeters in its greatest diameter. The lowermost part was level with the brim of the pelvis and beneath the cyst itself in the pouch of Douglas were several coils of small intestine. The cyst was twisted on its pedicle one and a half times. There was thrombosis of the veins in the pedicle. The right cystic mass including the tube was removed and routine appendectomy done.

Clinical Diagnoses

Acute appendicitis.
Twisted ovarian cyst?

Dr. Richard Dwight's Diagnosis

Acute appendicitis.

Pathologic Diagnoses

Dermoid cyst of the ovary with some teratomatous elements.
Healed appendix.

Pathologic Discussion

Dr. Tracy B. Mallory: The specimen which reached us was a fairly large cystic ovary obviously gangrenous from interference with the blood supply. When opened it proved to be filled with hair and cheesy material and down at one corner, as there so often is in dermoid cysts, there was a solid nubbin of tumor in which cartilage and various other teratomatous elements were discovered. The appendix was entirely negative histologically. Teratomas of the ovary ordinarily provoke symptoms at a very much earlier age period than was the case in this woman. You find them not uncommonly in children, frequently in young women and only rarely in elderly women past the menopause.

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ADVANCES IN THE SPECIFIC TREATMENT OF PNEUMONIA

IN a recent issue of this *Journal* (Nov. 5, p. 890) the Pneumonia Committee of the Boston Health League called attention to the approaching season of increased prevalence of lobar pneumonia. The committee emphasized the importance of this disease and the usefulness of specific treatment, and also outlined the facilities available in Boston for rapid typing, for obtaining Types I and II antipneumococcic serum and for the nursing care of pneumonia patients.

These conveniences are not limited to Boston. There are now about seventy-five laboratories throughout Massachusetts prepared to do rapid sputum typing and to furnish serum for the treatment of early cases in which Type I and II pneumococci are found. Nursing service is also available on a visit basis in almost every part of this state. In many other states in New England and elsewhere, increasing numbers of laboratories in large and small communities are equipped to do rapid sputum typing. The health authorities of a number of these states have made provisions for typing and will supply serum out of public funds, under certain specified conditions. Every physician will do well to acquaint himself with the particular facilities available in his own community.

The fullest benefit of specific serum treatment in pneumonia, namely, the marked reduction in mortality, the induction of an early crisis and probably the prevention of empyema, can be attained only when cases of the proper type are treated early. This means that the physician must make every effort to obtain an etiologic diagnosis in every patient *as soon as the diagnosis of pneumonia is suspected.* Practically, this means the typing of sputum from every patient presenting an abrupt onset of a febrile illness accompanied by chill, pleuritic pain, cough and blood-tinged or rust-colored sputum. Moreover, the regularity with which the finding of Type I or II pneumococci in the sputum of such cases is associated with the clinical picture of lobar pneumonia makes this procedure all the more valuable. To wait for the distinctive physical signs of pulmonary consolidation to become apparent, therefore, means the loss of valuable time. Repeated sputum examinations are desirable when the earlier samples are unsatisfactory or fail to yield a definite type.

The classification of the pneumococci formerly included in Group IV into the specific Types IV to XXXII, inclusive, has had a number of practical effects. It has made it possible to obtain a definite type diagnosis in those cases in which a doubt might otherwise exist when a pneumococcus could not be classified as Type I, II or III. It has enabled workers in some large clinics and others interested in the treatment of large numbers of pneumonia patients to ascertain the relative importance of the various types. This, in turn, has served as a guide for the further development of specific serums.

The practical results of this course of events are already becoming apparent. Bullowa, at the Harlem Hospital, has obtained highly promising results in the treatment of cases due to at least four of the more frequent of these new types, namely, Types VII,[1] VIII[2] and XIV[3] and, more recently, Type V.[4] In this issue of the *Journal*, Finland and Tilghman have presented a series of carefully studied cases of Type V pneumonia treated with a specific antibody at the Boston City Hospital. The result of the therapy in this small group of cases appears to be very favorable and is comparable to the results in specifically treated Type I cases. The latter writers have also had similar experience with the treatment of cases of Type VII pneumococcus pneumonia.[5]

These results appear to be definite advances

in expanding the field of usefulness in the specific treatment of pneumonia. They further emphasize the importance of rapid typing. It may not be amiss to suggest that Types V and VII be included in routine typing practice and that certain cases due to these types be considered for serum treatment. Specific serums for Types V and VII are not supplied at present by the Massachusetts Department of Public Health. They are being furnished in some other communities under the same conditions as Type I or II serum and may be obtained from certain of the commercial manufacturers.

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THE INCOMING EDITOR OF *THE NEW ENGLAND JOURNAL OF MEDICINE*

In the conduct of any human enterprise changes are inevitable and the editorial management of *The New England Journal of Medicine* passes, with the last issue of 1936, to Dr. Robert N. Nye who has been appointed Editor of this *Journal* by the Committee on Publications of the Massachusetts Medical Society to succeed Dr. Walter P. Bowers who has occupied the position of Managing Editor since April, 1921.

The retiring Editor wishes to express his appreciation of the support given by the Committee on Publications, the cooperation of the *Journal* Staff and the Officers and Fellows of the Massachusetts Medical Society during these years.

The official association of the *Journal* with the Massachusetts Medical Society was inaugurated on June 10, 1914, when the Council of the Massachusetts Medical Society voted to enter into an affiliation with the *Journal*, then the *Boston Medical and Surgical Journal*, thereby making the *Journal* its official organ. An Editorial Board was installed consisting of E. W. Taylor, Editor-in-Chief, with Robert M. Green his associate representing the owners of the *Journal*, and Walter L. Burrage and Frederick T. Lord representing the Massachusetts Medical Society. Cooperating with the Editorial Board, an Advisory Committee was created consisting of Edward C. Streeter, Chairman; Walter P. Bowers, Homer Gage, Joel E. Goldthwait, Lyman A. Jones, Hugh Williams, Alfred Worcester and Robert B. Osgood. This organization was continued with a few changes in the Editorial Staff and the Advisory Committee until April 21, 1921 when, after negotiations with the owners of the *Journal*, it was sold to the Massachusetts Medical Society and the Managing Editor was installed, with an Editorial Staff of nine doctors representing medical education in Boston. Additions have been made to the Staff from time to time, by the selection of physicians who are especially qualified to promote the value of the *Journal* to its readers.

The retiring Editor feels warranted in assuring the medical profession that the Staff will persist in its ambition to maintain a *Journal* of educational value and worthy of the respect of its sister publications.

Dr. Nye, the incoming Editor, is a graduate of Harvard College and the Harvard University Medical School and served as intern at the Massachusetts General Hospital and later as Research Assistant of Dr. F. T. Lord. His subsequent appointments have been Assistant Pathologist in the Pathological Laboratory of the Boston City Hospital, Assistant Director of the Antitoxin and Vaccine Laboratory of the Massachusetts Department of Public Health, Assistant and Associate at the Thorndike Memorial Laboratory of the Boston City Hospital, and for the past several years Assistant Pathologist in the Pathological Laboratory of the Boston City Hospital in charge of bacteriology.

In these several scientific fields Dr. Nye has been in close association with research and clinical medicine and is especially interested in the application of scientific knowledge to the practice of medicine. It is a privilege to commend him to our subscribers.

CHANGES IN THE DEPARTMENT OF MENTAL DISEASES

The nomination of Dr. David L. Williams to the position of Commissioner of Mental Diseases has been confirmed by the Council, and Dr. John V. Thuot has been appointed by Commissioner Williams to fill the position of Superintendent of the Boston State Hospital to supplant Dr. James V. May.

The Massachusetts Medical Society, through its officers, made certain recommendations to his Excellency respecting the qualifications of psychiatrists worthy of appointment to these positions but without suggesting the names of individuals. The purpose of the Society was to give assistance to the Governor if he wished for expert advice. These appointments were not made from practitioners eminent in institutional psychiatry so far as we have been able to learn.

THIS WEEK'S ISSUE

CONTAINS articles by the following named authors:

LANDSTEINER, KARL. Sc.D., M.D. Medizinische Fakultät der Universität Wien 1891. Member of the Rockefeller Institute for Medical Research, New York City. His subject is "Serological and Allergic Reactions with Simple Chemical Compounds." Page 1199. Address: 66th Street and York Avenue, New York City.

SHIGA, KIYOSHI. M.D. Tokyo University Medical College. S.D. Harvard. Formerly, Professor, Keio University; Dean of the Medical Faculty, and President of the Keijo Imperial University. Now, Professor of Medicine, University of Tokyo. Honorary Member of Kitasato Institute (for Infectious Diseases), Tokyo. His subject is "The Trend of Prevention, Therapy and Epidemiology of Dysentery Since the Discovery of Its Causative Organism." Page 1205. Address: University of Tokyo, Tokyo, Japan.

FINLAND, MAXWELL. B.S., M.D. Harvard University Medical School 1926. Instructor and Francis Weld Peabody Fellow in Medicine, Harvard University Medical School. Assistant Physician, Thorndike Memorial Laboratory, Boston City Hospital. Address: Thorndike Memorial Laboratory, Boston City Hospital, Boston, Mass. Associated with him is

TILGHMAN, R. CARMICHAEL. A.B., M.D. Johns Hopkins University School of Medicine 1932. Formerly, Research Fellow in Medicine, Harvard University Medical School. Assistant Resident Physician, Thorndike Memorial Laboratory, Boston City Hospital. Now Resident Physician, Johns Hopkins Hospital. Instructor in Medicine, Johns Hopkins University School of Medicine. Address: Johns Hopkins Hospital. Baltimore, Md. Their subject is "Clinical and Immunologic Observations in Cases of Pneumococcus Type V Pneumonia Treated with Specific Antibody." Page 1211.

KIMPTON, ARTHUR R. M.D. Dartmouth Medical School 1905. F.A.C.S. Surgeon-in-Chief, First Surgical Service, Boston City Hospital. Consulting Surgeon, Newton Hospital. Address: 23 Bay State Road, Boston, Mass. Associated with him is

DALRYMPLE, SIDNEY C. M.D. Bowdoin Medical School 1917. Diploma in Bacteriology, London University 1935. Associate Professor of Pathology and Bacteriology, Tufts College Medical School. Pathologist, Newton Hospital. Address: The Newton Hospital, Newton Lower Falls, Mass. Their subject is "Aneurysm of an Intestinal Branch of the Superior Mesenteric Artery." Page 1221.

SHEDDEN, WILLIAM M. M.D. Harvard University Medical School 1920. F.A.C.S. Assistant in Anatomy, Harvard University Medical School. Instructor in Surgery, Tufts College Medical School. Chief of Tumor Clinic, New England Medical Center. Assistant Surgeon to Outpatients, Massachusetts General Hospital. His subject is "Lymphatic Metastasis in a Case of Rectal Adenocarcinoma Simulating a Clinically Benign Tumor." Page 1222. Address: 270 Commonwealth Avenue, Boston, Mass.

ARNOLD, J. O. M.D. Jefferson Medical College 1896. F.A.C.S. Professor of Obstetrics, Temple University School of Medicine, Philadelphia, Pa. His subject is "More Rational Methods in the Prevention and Control of Eclampsia." Page 1226. Address: 4149 N. Broad Street, Philadelphia, Pa.

MISCELLANY

LUNCHEON IN HONOR OF MISS EMILY P. BISSELL

"Tuberculosis Then and Now" was the program theme of an honorary luncheon to Miss Emily P. Bissell, founder of the tuberculosis Christmas Seal. It took place Friday, December 11, at the Twentieth Century Club, Boston, with Dr. Frederick T. Lord, President of the Massachusetts Tuberculosis League, presiding.

"Tuberculosis Then" was presented by Dr. Horace Paine Stevens, who told how his father, Dr. Edmund Horace Stevens, contracted tuberculosis and was cured in 1863. The elder Dr. Stevens, aged 91 on January 2 next, sent regrets on his inability to attend.

Dr. Horace Stevens reported that Dr. Henry I. Bowditch successfully treated his father who had hemorrhages and fell in weight to 110 pounds. The treatment was as follows:

1. Life out of doors, and in the sunlight as much as possible.
2. Walking daily up to four miles, if the patient could do it.
3. Much sleep—early to bed and late to rise.
4. Extra food, with stress on milk and meat.

The old-fashioned stethoscope, with a cap on either end, was used by Dr. Bowditch. It was not very different from the instrument then but recently invented by Laennec.

As this was 19 years before Dr. Robert Koch of Germany discovered the tubercle bacillus and wrote his paper "Discovery and Cultivation of the Bacillus Tubercle", there was no knowledge of the cause of the disease, or of its communicability. It was held that severe and frequent colds caused one to "go into decline" or to have consumption.

During the Civil War Dr. Stevens was wounded in a naval engagement at the Battle of Mobile Bay. After his demobilization and his recovery he joined

the army but was soon out with the war's end. He at once became a student at Harvard Medical School, graduating in 1867. He has been a member of the Massachusetts Medical Society since 1868. In 1871 he settled in Cambridge, where he has remained and practiced ever since. The writer recently noted the sign of father and son on their joint Cambridge office.

Dr. Horace Stevens said that his grandfather, also a medical practitioner, and his father had come to believe in the communicability of tuberculosis through their experiences with families wiped out by the disease. While Dr. Bowditch was at first unfavorable to this idea, he later held the disease to be communicable.

"Tuberculosis Now" was presented by Dr. Alton S. Pope, Director of the Division of Tuberculosis, State Department of Public Health.

"If the 1900 death rate continued," said Dr. Pope, "the present tuberculosis deaths in Massachusetts would be 7,000 instead of 1,960."

After showing that tuberculosis has been reduced approximately 75 per cent since 1900, falling from the first to the seventh place among causes of death, he spoke of the accomplishment in sanatorium bed provision in Massachusetts which now has some 2½ tuberculosis beds per annual deaths. He declared that artificial pneumothorax even though some are now holding to the contrary, is definitely contributing to "arrest in tuberculosis patients" and that by stopping the spread of infection through sputum, is helping to reduce the number of cases. Dr. Pope stated that we may look forward to a time when tuberculosis may be said to be under control. Another authority has pointed out that control may be said to have arrived when the yearly mortality rate falls below 10 per 100,000 of the population.

When in 1904 the National Tuberculosis Association decided to do research and have applied the existing knowledge of tuberculosis, it also undertook the task of spreading information to all of the public. Without this the research would have been without ultimate value for after sanatoria, clinics and public health nursing are provided there remains the necessity of securing the individual's own willingness to do his part.

"It is in this field," said Dr. Pope, "that the funds from the Christmas Seal, founded by Miss Bissell, are able to make a most important contribution to tuberculosis prevention."

The guest of honor, Miss Emily P. Bissell, told how thirty years ago she founded the Christmas Seal to help finance a struggling tuberculosis hospital started by four physicians of Wilmington, Delaware. Though the need was large, the patients could not pay for their care and only eight remained in the sanatorium. Miss Bissell credited Einar Holboell, a postal clerk of Copenhagen, Denmark, with starting the first tuberculosis Christmas Seal in the world in 1904. She learned of his idea through Jacob Riis, who wrote about it in the *Outlook*. That the Seal is and always was primarily an educational device with the securing of financial income second in importance, Miss Bissell stoutly contended. Yet this financial figure since 1907 brought in approximately eighty million dollars.

The Christmas Seal message and the importance of tuberculosis and its preventability reached the legislators and they have acted. In Delaware the women who then backed the Christmas Seal Sale were Red Cross and Women's Clubs. Several legislators reported that their wives refused to get them supper whenever they declined to vote for an appropriation for the Delaware Commission so it had $15,000 yearly for many years until the State Board of Health was able to assume the duty and later to receive from the Delaware Tuberculosis Society its struggling sanatorium. It has now been improved by the state beyond recognition.

In closing, Dr. Lord stated that future methods of tuberculosis work were not considered. He believed, however, that the tuberculosis associations would find their chief field in improving and extending the health education work against tuberculosis and in cooperating with the various official agencies in an increasingly successful conduct of school chest clinics and the case-finding efforts that properly accompany it.

Unique at this luncheon was an exhibit of American and foreign Christmas Seals. It backed Miss Bissell and extended for 80 feet along the wall, filling the range of vision. Besides the vote of congratulation passed for Dr. Edmund Horace Stevens, was one of thanks to Mr. Preston C. Pond of Chicopee, for the loan of his international collection of Christmas Seals. The exhibit gave the audience a feeling that tuberculosis is not only being vigorously attacked throughout our own state and nation, but that the double-barred cross and the Christmas Seal are the world-wide emblems of a winning world-wide fight against tuberculosis.

AN EPIDEMIC OF SMALLPOX

Forty cases of smallpox in Danville, New York, have been reported by the local health officer with an extension of the epidemic to Hornell of five cases and to Ossian of two others.

The usual precautions are being taken in general vaccination of the people of those towns. Fortunately the disease has been mild and the epidemic seems to be under control.

MAINE NEWS

Since the first of March, in accord with the act, funds have been allocated to the Maine State Bureau of Health to expand and extend the work in Maternal and Child Health.

The extension of the service has called for a division of the work which has, heretofore, been carried on by the Division of Public Health and Nursing. The Maternal and Child Health Program has been placed under supervision of a recent appointee to the State Bureau, Herbert R. Kobes, M.D.

As plans for the enlarged program unfolded, the State Director of Health requested the President and Councilors of the Maine Medical Association to appoint an advisory committee to consult with Dr. Kobes on general policies. In addition to the four medical members of the Committee two dentists have been appointed, two public health nurses and a member of the State Bureau of Social Welfare. As the program expands, a large committee with many members from the State Medical Association will be organized to help carry the benefits of the services into all parts of the State. Below are described by Dr. Kobes in some detail the attitudes and plans of his department.

"Most of the field work will, of course, have to be carried on by public health nurses. But in no case is any nurse connected with the State Bureau of Health to carry on any work with a patient of a doctor unless that doctor is fully cognizant of what is being done. It would be well if in all cases this public health nurse could act as the private nurse of the physician. It must be remembered in this connection that public health nurses do public health nursing and not actual nursing of the sick. Their function, as is true of all public health bodies, is educational and preventive in nature.

In conformity with the present custom prenatal, infant, preschool and school nursing will be carried on by the public health nurses and an endeavor is being made for these nurses to cover the whole State. This program is well under way now because both the Maine Public Health Association and the American Red Cross are making plans by which their nurses and the State nurses will work together to carry out a well-conceived program for the whole family.

The Medical Director of the Program feels that wherever possible, health work with mothers and children should be carried on and directed by the family physician but that he should have some person to whom he may go in order that difficult problems may be answered for him. Thus, the Director of the Program works in an advisory capacity. It is known that there are many people within the State who cannot afford to pay for a physician's services. This is true of therapeutic medical service and naturally is even more true of health services. The physician has been and always will be willing to carry on a certain amount of work without any thought of financial recompense, but this type of work may take up too much of his time. In cases where people are unable to pay for medical services, the most economical method of taking care of these people must be considered. Knowing this, the necessity for infant and preschool conferences is obvious. The present program makes it possible to include limited numbers of such conferences at which attempts will be made to have a local physician in attendance and for this service he is to be paid a nominal fee.

Certain sums have been set aside for postgraduate work for the medical and dental professions. The Maine Dental Association, through its advisory committee to the Maternal and Child Health Program, is making arrangements for a course to be held early this fall at which a dental authority will take up problems connected with children's dentistry. Likewise, steps are being taken to develop a course which includes the fundamentals in obstetrics and pediatrics. It has been thought best that this course should be carried on by men practicing within the State—who are especially qualified in these two fields, Roland B. Moore, M.D. of Portland, and Magnus Ridlon, M.D. of Bangor with their associates will conduct the obstetric sessions and Thomas A. Foster, M.D., of Portland, and Clair Bauman, M.D., of Waterville, and their associates, will conduct the pediatric sessions. These courses are to be given in rural areas, because the program as a whole is one for these areas. It will be possible for the rural practitioner to attend the postgraduate courses near his home. Arrangements for the course will be made through the various county medical societies who will sponsor the courses. They will be assisted, so far as expenses are concerned, by the Division of Child Hygiene."

In addition to the services described by Dr. Kobes, medical consultation is offered by him. For families unable to meet the expense of a consultation for their child, Dr. Kobes will be prepared to give his services at the bedside, over the telephone or through the mail.

A most excellent program was presented during the two days. It represented a vast amount of work, hard work, and planning by those responsible, and to the profession as a whole we owe and give deserved thanks. To us these important sessions demonstrate a fact worth notice. Maine is essentially a rural state. Large medical centers do not exist and the men conducting these clinics are not primarily teachers; they are men who earn their bread and butter by the daily practice of medicine. What they do, and how, is decidedly well worth knowing and anyone who failed to benefit at the last session is unfortunate to say the least.

To the credit of the Waterville group, several of the younger men were given places on the program. They did their work most creditably and showed a development of that most needful of all things; clinical sense and judgment. It was also very evident that the men in attendance appreciated the various clinics as was shown by the worth while keen discussion and questions. The clinics showed that the men giving them realized the fact that they were to talk to others doing the same things. Their ideas were put over clearly and were to the point.

Cancer Clinics

The *Journal* is pleased to announce that four hospitals, The Maine General at Portland, The Central Maine General at Lewiston, The Eastern Maine General at Bangor and the Thayer Hospital at Water-

ville, have established active cancer clinics. This is an extremely important move in the right direction and deserves and should have the hearty support of the profession.

Sponsored and advocated by the Maine Medical Association, these clinics offer the practitioner the services of the staff to establish the diagnosis and to institute the indicated treatment at the desire of the referring physician. As we stand today we know that certain types of malignancy in certain organs or tissues are best treated by radical surgery. It would seem that almost the ultimatum had been reached so far as operative removal is concerned, but there are types of malignancy situated in certain organs and locations that are seemingly, with our present knowledge, best treated by radium or deep x-ray therapy.

The responsibility of the general practitioner in establishing the diagnosis of malignancy is great. It is not expected that he will be asked to make technical examinations far beyond his ability and equipment, but he can and should, in suspicious cases, avail himself of every possible aid. That is the main object of the cancer clinics. It is to help physicians in their daily work, to establish the diagnosis early so that proper measures, so far as we know them, can be put into effect. The clinics will be staffed by a surgeon, internist, pathologist and radiologist. With the spirit always shown by medicine to those unable to assume the financial burdens, the clinics offer this valuable service. The family or attending physician is urged to come with his patient. What he knows may be and often is of great help, the consultation will not be so complete as it should without him, and the disposition of the given case will be as he elects.

The surgeon of experience knows today the chances of cure, if the term be permissible, of malignancy of some organs and at certain stages. We do not as yet know the full value of radium or deep x-ray therapy in others, but as the various types are grouped and treated, an honest evaluation of the end-results can be helpful. What not to attempt is sometimes valuable to know. Clinics are powerless unless the work is supported by the profession as a whole. The fight properly begins with the family physician—as a rule he sees the case early, and he must, beyond a reasonable doubt, prove the suspicious case one way or the other. If he does, then many, many times the end-result is a happy one.

Diagnostic and consultation clinics for cancer will be held at the following hospitals on the day and at the hour mentioned:

Maine General, Portland; Surgical Director, William Holt, M.D.; Thursday, 11 a. m.-12 m.

Central Maine General, Lewiston; Surgical Director, Joseph Scannell, M.D.; Tuesday, 11 a. m.-12 m.

Eastern Maine General, Bangor; Surgical Director, Magnus Ridlon, M.D.; Thursday, 11 a. m.-12 m.

Thayer, Waterville; Surgical Director, Edward H. Risley, M.D.; Thursday, 9-11 a. m.

THE PHARMACOPOEIAL HEARING

As widely announced, the members of the Executive Committee of Revision of the Pharmacopoeia held a hearing and conference in Washington on November 30 and December 1. The titles under review for possible revision and republication in the "First U.S.P. Annual Supplement", to appear on January 1, 1937, had been announced some weeks before. These were widely published in the pharmaceutical press and sent by direct mail to all who expressed an interest.

In the meantime the Sub-Committees had studied the proposed modifications and submitted a number of recommendations. These were embodied in page proof, which was distributed about ten days before the hearing. This page proof became the subject of first consideration at the hearing, and each monograph was specifically discussed.

The success of the plan is assured by the great interest and large attendance, and the splendid spirit of cooperation. The members of the U.S.P. Committee on Revision entered freely into the discussions describing many experiments and the results of their investigations. The discussions were stenographically reported and will be made available to all members of the Committee on Revision and those who were present.

There were three public sessions, continuing until late on the evening of November 30. On Tuesday, December 1, the members of the Executive Committee of Revision met with the officials of the Food and Drug Administration and informally discussed the proposed revision of U.S.P. monographs. In the afternoon the members of the Committee of Revision reassembled and in the light of all facts made available by previous studies and conferences, decided on practically all changes to be submitted to the General Committee of Revision for approval and for publication in the "First Annual Supplement" to the Pharmacopoeia.

This Supplement will be well printed and bound in pamphlet form, having the general appearance of the Pharmacopoeia. This pamphlet, of approximately 100 pages, will be available only in a substantial spring binder, the binder being usable subsequently for future reprints.

No price has yet been fixed for the Supplement and binder, but it is expected that this will be maintained at approximately the cost of preparation.

E. FULLERTON COOK,
Chairman of the U.S.P. Committee of Revision.

CORRESPONDENCE

TEACHING PSYCHIATRY TO HOUSE OFFICERS*

Dear Mr. Editor,

Today it is very generally acknowledged that in the treatment of many patients, more is accomplished from the recognition and proper management of their mental conflicts than from the diagnosis and treatment of their somatic disturbances; not infrequently in our patients no organic disease is primarily responsible for their complaints. To put it another way, mind plays a large part in the mechanism of illness. All of this calls for a better knowledge of psychiatry on the part of practitioners than most of them have.

How to correct this situation is an important pedagogic problem of today. Better teaching of psychiatry is now being given in our medical schools, but this is not enough.

With a realization that patients at the Peter Bent Brigham Hospital would be better treated, if those primarily responsible for their care knew more of the fundamental principles of psychiatry, I sought a means to that end. It was obvious to me that these house officers should have an opportunity to see and follow the management of mental patients in an institution planned for that purpose. How could this be brought about at no cost to the Peter Bent Brigham Hospital?

I first took this problem to Dr. James V. May, Commissioner of Mental Diseases of the Commonwealth and later to Dr. Winfred Overholser his successor. Both were willing, actually eager, to cooperate, with the result that they offered to my medical house officers at the Peter Bent Brigham Hospital the opportunity of residence and practical instruction for 4 months in Massachusetts State Hospitals. I incorporated in my medical service of 16 months, an additional period of 4 months to be spent at one of these State Hospitals, the period following a 4 months' experience in clinical laboratory work and preceding clinical service at the Peter Bent Brigham Hospital.

Now this plan has been in operation for a year, two men going to the Boston State Hospital and one to the Worcester State Hospital for each period. What is the result? A noticeable increase in interest in the mental conflicts of our patients and a greatly bettered method of handling their psychiatric problems. It has proved definitely worth while to Brigham patients, and I am sure it will be a continuous help to these house officers in their subsequent practice of medicine. The officers of these institutions have been enthusiastically concerned to see that these house officers learn as much as possible of psychiatry in the available time.

This plan is a practical means of meeting another deficiency in our scheme of educating men to practice a better medicine. Undoubtedly in the long run this plan, too, will bring a recompense to state hospitals for mental diseases in developing practitioners ready to be more cooperative in meeting the enormous problem of the best possible care of patients afflicted with serious mental diseases.

HENRY A. CHRISTIAN, *Physician-in-Chief,*
Peter Bent Brigham Hospital, Boston, Mass.

*A letter to the Editor of the American Medical Association. J. A. M. A. 107:2069 (Dec. 19) 1936.

OFFICIAL ACTIONS OF THE BOARD OF REGISTRATION IN MEDICINE

State House, Boston

December 11, 1936.

Editor, *New England Journal of Medicine,*

This is to inform you that at the meeting of the Board of Registration in Medicine held December 10, 1936, it was

Voted: To restore the license of Dr. Julius Saipe, 218 Highland Avenue, Somerville, Massachusetts.

Voted: To revoke the registration of Dr. Henry Daniels of Brockton, and to cancel his certificate of registration for the practice of medicine in the Commonwealth of Massachusetts, because of court conviction on a charge of abortion.

Voted: To revoke the registration of Dr. Barney Edward Sachs of Worcester as a practitioner of medicine in this Commonwealth, and to cancel his certificate of registration, because of acting as principal or assistant in the carrying on of the practice of medicine with an unlicensed person.

Voted: To suspend for six months the registration of Dr. Arthur E. Brides of Stoughton, because of gross misconduct in the practice of his profession.

Yours very truly,
STEPHEN RUSHMORE, M.D., *Secretary.*

A CORRECTION OF FIGURES IN THE 1935 REPORT OF THE BOARD OF REGISTRATION IN MEDICINE

Board of Registration in Medicine
State House, Boston

December 14, 1936.

Editor, *New England Journal of Medicine,*

The Annual Report of the Board of Registration in Medicine for the year ending November 30, 1935 on page five has a statement that the average rating on first examination of the fifty-four candidates who were graduates of Tufts College Medical School was 69. On page six is the statement that of sixty candidates who were graduates of Tufts College Medical School, 45 passed, 15 failed, giving a percentage of 25 for rejected candidates.

Although these tables are not quite comparable, a discrepancy is apparent and the marks were rechecked and the computation done a second time. Apparently in transferring the marks from one paper to another, a mistake occurred and the figures on page five for Tufts College Medical School should read that the average rating of the fifty-four can-

didates who took the examination for the first time was 76.

Will you be kind enough to publish this letter, as an apparent injustice has been done to the school.

Yours very truly,

STEPHEN RUSHMORE, M.D., *Secretary.*

ARTICLES ACCEPTED BY THE AMERICAN MEDICAL ASSOCIATION COUNCIL ON PHARMACY AND CHEMISTRY

535 North Dearborn Street, Chicago, Illinois,
December 27, 1936.

The New England Journal of Medicine,

In addition to the articles enumerated in our letter of November 3 the following have been accepted:

Abbott Laboratories
- Sterile Ampoules Procaine Hydrochloride Crystals for Spinal Anesthesia, 50 mg.

Lederle Laboratories
- Tablets Digitalis Whole Leaf—Lederle, ¾ grain
- Tablets Digitalis Whole Leaf—Lederle, 1 1/2 grains
- Tablets Digitalis Whole Leaf—Lederle, 3 grains

McKesson & Robbins, Inc.
- McKesson's Halibut Liver Oil with Vitamin D Concentrate in Neutral Oil, Capsules, 3 minims
- McKesson's Halibut Liver Oil Plain, 1 cc.
- McKesson's Halibut Liver Oil Plain, Capsules, 3 minims

Sharp & Dohme, Inc.
- Scarlet Fever Streptococcus Toxin for Immunizing—Mulford
- Scarlet Fever Streptococcus Toxin for the Dick Test—Mulford

The following product has been accepted for inclusion in the List of Articles and Brands Accepted by the Council But Not Described in N. N. R. (New and Nonofficial Remedies, 1936, p. 471):

Belle Alkali Co.
- Dichlormethane Solvent

Yours sincerely,

PAUL NICHOLAS LEECH, *Secretary.*

"A PREFACE TO NERVOUS DISEASE"

December 11, 1936.

Editor, *New England Journal of Medicine,*

A worker in another limited field has been reading "A Preface to Nervous Disease" by Dr. Stanley Cobb: a small book of some one hundred and seventy pages interspersed with clear diagrams and helpful charts. This worker wishes to report pleasure in the reading and to acknowledge a remaining sense of obligation for new knowledge acquired which should enable him to serve his patients better.

The diction of the book is delightful. Again and again a technical passage is followed by a graphic summary almost novelesque in style, which dissipates possible fatigue and stimulates new concentration. For example, in speaking of the underlying segmentation of the brain stem, I olfactory, II optic, III and IV oculomotor, V biting, VI, VII and VIII sentinel, IX, X, XI and XII nutritional, he fancies a predatory animal in search of game. "First the trail is picked up by the olfactory sense (I); after following perhaps for hours, the game is viewed (II) and the chase starts in earnest. At close quarters the dodging and quick movements of the prey can only be followed by quick movements of the eyeballs (III, IV). At last the prey is in reach and with a swift bite (V motor), guided by the special whiskers or vibrissae about the mouth (V sensory), the quarry is seized, and so forth." Again in Chapter VI, dealing with the cerebral circulation, in describing ill-defined intercellular fluid spaces about capillaries and nerve cells, he says, "Fluid moves through it but meets a certain amount of resistance, like water flowing through heavy swamp vegetation, not running like a brook." A striking visualization.

The author's great familiarity with neurologic literature and research, old and new, is evident. There is a vast amount of well-presented information which will make it possible for general practitioners and specialists in other fields to detect neurologic symptoms and signs more easily and to interpret their significance more reliably.

We have the strong impression that there is much original thought in these pages, although this originality is disguised rather than proclaimed. Wide circulation should be the fate of the book and we are sure that, thanks to the author for his effort, will be general and genuine.

R. B. O.

RECENT DEATHS

CRAWFORD—LAWRENCE PEARS CRAWFORD, M.D., of 75 Elm Avenue, Wollaston, died at the Faulkner Hospital, Jamaica Plain, December 12, 1936. He was born in 1875, graduated from The Rush Medical College, Chicago, in 1904 and had practiced in Wollaston for the past 19 years.

Dr. Crawford was a Fellow of the Massachusetts Medical Society (having joined in 1918) and the American Medical Association.

He is survived by his widow, Mrs. Dorothy Crawford; a daughter, Miss Mary E. Crawford, a student in Wellesley College, and three sons, Eugene and William Crawford of Chicago, and John, a student at Thayer Academy.

BRINDISI—ROCCO BRINDISI, M.D., with an office at 149 Richmond Street, Boston, died suddenly December 14, 1936, aged 76 years. Dr. Brindisi graduated from the University of Naples and practiced for a time in Italy before coming to Boston. In addition to an active practice among the Italian people, he served as Italian consul until 1902.

He joined the Massachusetts Medical Society in 1906. He was a Knight and Officer of the Crown of Italy, chairman of the Roman Legion of America during the World War, president of the Societa Dante Alighieri and had served the United States

federal education board and was responsible for the formation of evening classes for teaching the Italian language.

His widow, Mrs. Sophia (Buonamici) Brindisi, survives him.

PERRY — CHAUNCY VALENTINE PERRY, M.D., of Greenfield, Massachusetts, was found dead in his room at the Weldon Hotel, December 8, 1936. Dr. Perry was born in 1900, graduated from the Massachusetts State College in 1924 and from the Harvard Medical School in 1928. He had served an interneship at the Boston City Hospital and the Boston Lying-in Hospital, and, after settling in Greenfield in 1931, was retained by several insurance companies as medical examiner and carried on an active general practice.

Dr. Perry had served as town physician for one year. He was a Fellow of the Massachusetts Medical Society and the American Medical Association.

Two brothers, Nelson Perry of Waltham and John Perry of Manchester, Vermont survive him, as does a sister Mrs. Margaret Stone who lives in Colorado.

NOTICES

THE DIRECTORY OF THE MASSACHUSETTS MEDICAL SOCIETY

This publication is being compiled with all available information up to January 1, 1937. The material will be in the hands of the printer immediately after the first of the year and the copies will be distributed as soon as possible.

CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS, UNDER THE PROVISIONS OF THE SOCIAL SECURITY ACT

Clinic Date Orthopedic Consultant

Haverhill—January 6, 1937—Dr. Arthur T. Legg.
Brockton—January 14, 1937 — Dr. George W. Van Gorder.
Salem—January 4, 1937—Dr. Harold C. Bean.
Gardner—January 12, 1937—Dr. Mark H. Rogers.
Greenfield—January 8, 1937—Dr. Harry R. Wheat.
Pittsfield—January 18, 1937—Dr. Francis A. Slowick.
Springfield — January 20, 1937 — Dr. Garry deN. Hough, Jr.
Worcester—January 15, 1937—Dr. John W. O'Meara.
Lowell—January 30, 1937—Dr. W. Russell MacAusland.
Hyannis—January 26, 1937—Dr. Paul Morton.
Fall River—December 28, 1936; January 25, 1937—Dr. Eugene McCarthy.

ILLUSTRATED LECTURE AT THE ROBERT B. BRIGHAM HOSPITAL

Dr. Sumner M. Roberts and Dr. Robert J. Joplin will give an illustrated lecture on "Arthroplasty of the Elbow" Wednesday, January 20, at 8 o'clock at the Robert B. Brigham Hospital. The operative technic on nineteen postoperative cases will be shown.

Physicians and medical students are cordially invited.

ANNOUNCEMENT

ALBERT EDWARD SLOANE, M.D., announces the opening of an office at 416 Marlborough Street, Boston. Telephone: Kenmore 4140.

REPORTS AND NOTICE OF MEETINGS

THE NEW ENGLAND HEART ASSOCIATION

The monthly clinical meeting of the New England Heart Association was held at the Boston City Hospital on December 14. Dr. Soma Weiss presided.

Dr. Weiss opened the meeting with a demonstration of pathologic specimens. An instance of adhesive pericarditis was shown with Aschoff bodies in the myocardium but with competent valves. The patient had suffered from rheumatic fever and died following the first attack. Another specimen showing rheumatic involvement of all the cardiac valves was presented. The patient had had repeated attacks of rheumatic fever since the age of 17, and died at the age of 30. A specimen of coarctation of the aorta from a six months old fetus was demonstrated. Two specimens with perforated hearts from a solitary abscess were described. In one instance *Staphylococcus aureus* and in the other pneumococcus were the responsible factors. In both instances death occurred suddenly and rather unexpectedly. A case of subaortic stenosis with systolic thrill and murmur over the aortic area in a patient who died from pneumonia was shown. In another patient a similar condition existed but was complicated by subacute bacterial endocarditis, which involved the subaortic stenotic area, as well as the area below the pulmonary valve, that was considerably narrowed.

Dr. James G. M. Hamilton spoke on circulatory effects of nitroglycerine. Sixteen blood pressure and pulse rate observations were made on five subjects without cardiovascular disease and five patients with coronary sclerosis in the recumbent or semirecumbent position before and after the administration of nitroglycerine in doses varying from 0.33 to 5.2 mg. with an average of 1.75 mg. Systolic pressure fell on the average 8.8 mm. Hg. Diastolic pressure showed variable changes from slight increases in four cases to slight decreases in nine, no change occurring in three. Pulse rate increased on the average 14 beats per minute. These changes were considered to be less than might have been expected from the supposed pharmacologic action of the drug. A comparison was made between the untoward effects of nitroglycerine, one example of which was reported, and the artificial syncope induced after sodium nitrite. It was suggested that the reason for the former might be, as in the latter, a venous pooling dependent on an upright or semiupright posture and resulting in diminished venous return to the heart and cerebral ischemia.

The most constant changes in the electrocardiogram after nitroglycerine were obtained in the chest lead in which in all but one case, Q increased in amplitude by 10 per cent to 70 per cent, and in all but two, T decreased by 5 per cent to 26 per cent.

Dr. Edward A. Edwards discussed The Effect of Thrombophlebitis on the Venous Valve. The organization and subsequent recanalization of a *complete thrombus* produce a disruption of the venous valve. This thesis was investigated by following the histologic changes in artificially induced phlebitis in the dog and spontaneous phlebitis in the human being. It was found that the cusp may become incorporated into the new thickened intima. If it happens to lie in the center of the lumen at the moment of thrombosis, it undergoes complete or almost complete disruption. In either case the process finally produces a valveless vein.

Parietal thrombosis may similarly incorporate the cusp into the intima, or it may fill the sinus with connective tissue and thicken and shorten the cusp proper. Thus there is produced true stenosis and insufficiency.

When the thrombosed vein does not recanalize, its collaterals dilate. The valves of such collaterals are rendered incompetent by the dilation. In some situations, as in the inferior vena cava, this insufficiency allows the necessary reversal of the blood stream in the collateral veins.

It was felt that these studies revealed one of the causes for poor venous circulation after phlebitis.

A symposium on The Relation of the Nutritional Deficiencies to the Cardiovascular System was then presented. The first paper of this group was by Dr. James M. Faulkner, who spoke on Vitamin C and Rheumatic Fever. He referred to the work of Rinehart who had suggested an etiologic relationship between hypovitaminosis C and rheumatic fever. Other workers had not found vitamin C of any specific therapeutic value in rheumatic fever. On the other hand, there was abundant evidence in the literature that infectious diseases in general are a very important precipitating cause of scurvy. It had been suggested by some previous observations of Dr. Faulkner that rheumatic fever was no exception to the rule that infections throw a strain on the vitamin C metabolism. The development of methods of titrating ascorbic acid (vitamin C) directly in the blood serum and urine made it possible to attack this problem in a quantitative way. A comparison was made of the serum ascorbic acid levels in normal individuals, in scurvy, and in the presence of various infections. It was found that in scurvy the serum ascorbic acid is much reduced, averaging about one-third that found in normal individuals. In the presence of infection it was found that the serum ascorbic acid was also much reduced, averaging about one-half that found in normal persons. Patients with rheumatic fever showed a depression of the serum ascorbic acid level of similar magnitude to other infections. Balance studies were made in cases with infection in which known amounts of ascorbic acid were given in the diet while the serum levels and urinary output were followed. These studies indicated that, in the presence of infection, the intake of ascorbic acid necessary to raise the serum level and urinary output to normal is far greater than in normal individuals. The conclusion was that vitamin C does not play a specific role in the etiology of rheumatic fever but that rheumatic fever may, like many other infectious diseases, deplete the stores of vitamin C in the body.

Dr. Robert W. Wilkins spoke on the Clinical Features and Characteristics of the Heart and Circulation in Nutritional Deficiencies. Dr. Wilkins found that in patients with vitamin B deficiency diseases, such as alcoholic polyneuritis or pellagra, disturbances of the cardiovascular system are often found which cannot be accounted for on the basis of the etiologic factors commonly accepted as capable of producing circulatory failure. These disturbances are similar to those reported in beriberi and, it was postulated, are due to vitamin B deficiency.

Clinical symptoms and signs of heart failure often appear suddenly in patients deficient in vitamin B. Palpitation and dyspnea, especially on exertion, dependent edema, engorged veins, orthopnea or paroxysmal dyspnea may cause the patient to enter the hospital. On physical examination the heart may be slightly or moderately enlarged, and there is tachycardia, embryocardia and gallop rhythm. There is a prominent precordial and epigastric pulsation. Systolic and, rarely, diastolic murmurs may be heard. The electrocardiogram usually shows abnormal T waves, and prolonged Q-T interval. There is a general peripheral vasodilatation with flushed skin and warm extremities. The systolic blood pressure is normal or slightly elevated, and the pulse pressure is often increased. "Pistol shot" sounds may be heard over the large arteries. The circulation time is decreased, and the A-V oxygen difference is small. The venous pressure is usually elevated, and there may be marked peripheral edema. There is danger of sudden collapse and death.

With treatment by vitamin B (B_1) these derangements of the cardiovascular system revert to normal, sometimes quickly, in which case they may swing at first to subnormal, or slowly, even in spite of intensive treatment. Whether the return is quick or slow may depend on the severity of the structural changes before treatment, or on the deficiency, in some cases, or more than one specific substance.

Dr. Florence Haynes presented an electrocardiographic study of the heart in the vitamin B deficient rats. Eighteen rats were placed on a diet consisting of Wesson salt mixture 3.5 per cent, cornstarch 55.0 per cent, butter fat 8.5 per cent, washed casein 18.0 per cent, and bakers' yeast 15.0 per cent. The yeast was treated vigorously by autoclaving at a pH of 9, so that B_1 and possibly some other B factors were destroyed. Standardized electrocardiograms were taken on the extremities by means of skin electrodes of copper wire. Vitamin B deficiency in the rat is characterized by a gradual decrease in food intake and body weight and of fall in heart rate from 500 to about 350 beats per minute. In four-

teen of eighteen deficient rats, electrocardiograms showed definite T-wave changes consisting either of high waves with high origin or flat or inverted T-waves, often with low origin. Usually very high T-waves were observed only the first time the rat became deficient, succeeding deficiencies being accompanied more often by flat waves. The rate, as well as the complex changes, rapidly returned to normal with sufficient doses of crystalline vitamin B_1, with or without increase in the food intake. In two cases high T-waves became inverted for a short time after vitamin B_1 was given. In certain instances no T-wave changes appeared although the rate fell to the same low level which had previously been accompanied by abnormal T-waves.

In order to throw light on the mechanism of these cardiac changes, adrenalin and atropine were injected and vagus section was carried out on a few rats. Few changes in rate or in complexes were observed. This is in agreement with the statement of Drury, Harris and Maudsley that the bradycardia of vitamin B deficiency in rats, unlike the heart block produced in pigeons, is not of vagus origin.

The hearts of deficient rats were more sensitive to strophanthin than normal rats as indicated by depression of the ST interval or inversion of the T-wave. Two deficient rats died after one-fourth the dose which is fatal for normal rats.

Dr. Weiss continued the discussion on the Relationship of Vitamin Deficiency and Cardiovascular Dysfunction. He reported on a study of the water content of the right and of the left ventricles, as well as on the rectus muscle, in a group of patients exhibiting vitamin deficiencies, in a normal group, and a control group with organic heart disease. The studies failed to reveal any change in the water content of the cardiac or rectus muscle in the vitamin deficiency group. The weight of the heart may be normal or increased in vitamin B deficiency diseases (polyneuritis, pellagra, beriberi). Frequently, but not necessarily, there may be a dilation of the right side of the heart. "Intercellular edema," so-called, and a vacuolization of the muscle cells, as well as of the cells of the conductive tissue is frequently present. These latter findings are in accordance with the observation made by Wenckebach on the beriberi heart in Java. The observations at the Boston City Hospital, however, indicate that the findings are not specific in this condition, for similar findings were observed in control cases.

The electrocardiographic changes, as well as the manifestations of cardiac insufficiency and peripheral circulatory collapse, responded to rest, to diuretics, and to specific treatment with parenteral crystalline vitamin B_1, or to the oral administration of vitamin extract and a highly nutritious diet. In some of the cases the responses to vitamin B_1 and to vitamin extract were rather prompt and striking; in others, rather slow. At present it is not possible to formulate a definite conclusion as to the specificity of the treatment. It appears, however, that if the cardiac failure is of some duration and remains untreated, the response, even to crystalline vitamin B_1, may be slow. It has been observed that the parenteral administration of crystalline vitamin B_1 produced within 24 to 48 hours a marked appetite in deficient patients who suffered from anorexia of several weeks' duration. Further studies are now in progress.

THE AMERICAN ACADEMY OF TROPICAL MEDICINE

The third annual meeting of the American Academy of Tropical Medicine was held in Baltimore, Maryland, on November 18, 1936. Dr. Richard P. Strong, Professor of Tropical Medicine at the Harvard Medical School, delivered the President's Address upon "The Modern Period of Tropical Medicine." Dr. Ernest Muir of London, Secretary of the British Empire Leprosy Relief Association, delivered an address upon "Recent Progress in Tropical Medicine in India." Dr. W. A. Sawyer, Director of the International Health Division of the Rockefeller Foundation, was elected President for 1937. Dr. George C. Shattuck, Assistant Professor of Tropical Medicine at the Harvard Medical School, was elected a member of the Council. Dr. E. V. Cowdry, Professor of Cytology at Washington University, and Dr. Fred L. Soper, of the Rockefeller Foundation, were elected to membership, and Dr. W. Schüffner, Director of the Institute voor Tropische Hygiene in Amsterdam, was elected to honorary membership.

FAULKNER HOSPITAL CLINICAL MEETING

The regular monthly clinical meeting was held at the Faulkner Hospital on Thursday afternoon, December 3, at 5:00 p. m.

The first case was that of a baby who had died just after birth. The mother was a primipara and the baby had a face presentation. It was decided to do a version rather than a cesarean, which was successfully accomplished. The after-coming head was delivered by pressure on the fundus rather than by the application of forceps. The postmortem examination showed a tear in the tentorium on both sides with resulting hemorrhage. The point was brought out in the discussion that a certain percentage of breech presentations in primiparae are bound to end in fatality to the baby, but it was not felt for this reason that such cases should have a cesarean section done. It was also brought out that it is still an unsettled question whether it is better to exert pressure through the fundus or apply forceps.

The second case was that of a woman 76 years of age who had had indigestion over rather an indefinite time and had recently developed an increasing and painless jaundice. X-ray examinations of the gallbladder and gastro-intestinal tract were not of assistance in making a diagnosis and the patient was finally explored as a diagnostic procedure, but with the feeling that there probably was an inoperable cancer at the head of the pancreas and all that could be accomplished would be an anastomosis be-

tween the gallbladder and the small intestine. At operation, however, a small adenocarcinoma of the papilla of Vater was found which was excised and the pancreatic and biliary ducts reimplanted in the duodenum. This case illustrates the importance of using exploration as a diagnostic procedure in cases of complete obstructive jaundice in which a definite diagnosis cannot be made by other methods.

Following the presentation of these two cases a photograph of the hands of a surgeon who had been permanently crippled as a result of operating under the x-ray was shown. With the tendency to operate under the x-ray in fracture work, there are developing an increasing number of x-ray injuries among surgeons, and it is important for surgeons to realize how definite this danger is. Apparently there is a misunderstanding among surgeons in regard to what is meant by "shock-proofing an x-ray apparatus". Some surgeons think that this is a form of protection against x-ray burns, but it is only a protection against being electrocuted by the machine.

Following this Dr. Arthur T. Hertig gave an illustrated talk on "The Pathology of Abortions." He reported two hundred cases of which practically all were spontaneous abortions and called attention to the fact that 70 per cent of these were due to some defect of the embryo or of the membranes. He showed some interesting pictures of ova which had failed to develop and called attention to the fact that certain of these ova, which are blighted, tend to develop into moles the longer they stay in the uterus, and the moles tend to become malignant as time goes on. In view of the fact that, by the use of hormones, abortions are sometimes prevented, he raised the question as to whether it would not be better to let abortions occur and try for a subsequent pregnancy, in view of the fact that a beginning abortion may indicate a diseased ovum which will end in a congenital malformation of some sort, or possibly develop into a malignant mole. This idea did not appeal to some of the clinical obstetricians who emphasized the great number of patients who would go through a successful pregnancy and have a normal baby after having had, in the early months of pregnancy, a little flowing which quieted down under rest in bed.

Dr. Hertig felt that it was so unusual for a normal ovum to abort spontaneously that such an occurrence tended to arouse the suspicion of an artificial interruption of the pregnancy.

Of his cases 30 per cent of abortions were due to maternal causes and of these a reasonable number were due to low implantation of the ovum in the uterus. Here again the question was raised as to whether it would not be better to let such an abortion proceed after it started than to try to check it, because these are the cases which eventually lead to placenta praevia.

In the maternal causes, infection of one sort or another plays a part, and if these infections could be cleared up the abortions might be avoided. Of the whole series of sixty cases in which spontaneous abortions occurred due to maternal causes, in only 20 per cent could some procedure have been attempted which would have obviated the accident.

BOSTON UNIVERSITY MEDICAL SOCIETY

One of the country's foremost authorities on diabetes, Dr. Elliott P. Joslin, was the speaker at a meeting of the Boston University Medical Society, November 30, in the Evans Memorial Auditorium. Dr. Joslin's subject was "Recent Developments in the Treatment of Diabetes." Dr. Howard M. Clute of the faculty presided.

This was the second in a series of monthly meetings to be held by the recently formed Medical Society, which was inaugurated for the purpose of broadening the viewpoint of both medical students and physicians. Future meetings will be based on a wide variety of medical topics, of both immediate and future interest.

Dr. Joslin has been engaged in the practice of medicine in Boston since 1895, and has been connected with the Harvard Medical School since 1898 when he began his work as an assistant in physical chemistry. He has been clinical professor of medicine since 1922. Dr. Joslin is consulting physician at the Boston City Hospital. He is a Fellow of the American Academy of Arts and Sciences, and holds membership in the Association of American Physicians, the American Medical Association, and the American Philosophical Society. He is the author of "The Treatment of Diabetes Mellitus" and "A Diabetic Manual."

JOINT MEETING OF THE BOSTON COUNCIL OF SOCIAL AGENCIES AND THE BOSTON HEALTH LEAGUE

The Boston Council of Social Agencies and the Boston Health League will hold their Annual Meetings jointly on January 7, 1937, at the Hotel Vendome. Dinner, which is $1.50, will be served at 6:30 p. m.

The speakers, Dr. Henry D. Chadwick, chairman, and Dr. Gaylord W. Anderson, Secretary of the Massachusetts State Health Commission, will present a summary of the legislation which the Commission is introducing at the next session of the legislature. If the work of the Commission in recodifying the health laws of the state is to be effective, bills must be passed. Come and learn how you may help to secure the passage of this legislation.

You are cordially invited to attend. Please make your reservation by January 5. Make checks payable to the Boston Health League, Room 1104, 80 Federal Street, Boston.

SOCIETY MEETINGS, CONGRESSES AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING MONDAY, DECEMBER 28, 1936

Tuesday, December 29—

9:30 a. m. Massachusetts General Hospital. Thoracic Clinic. Ether Dome.

Wednesday, December 30—

8 a. m. Massachusetts General Hospital. Grand Rounds. Orthopedic Department.

†12 m. Clinical-Pathologic Conference. Children's Hospital Amphitheater.

4 p. m. - 5 p. m. Surgical Pathological Conference. Dr. Cutler and Dr. Wolbach, Peter Bent Brigham Hospital.

Thursday, December 31—

8 a. m. Massachusetts General Hospital. Circulatory Clinic Rounds.

*8:30 - 9:30 a. m. Exchange visit, Surgical and Orthopedic Staffs of the Peter Bent Brigham and the Children's Hospitals, held this week at the Children's Hospital.

11 a. m. Massachusetts General Hospital. Medical Grand Rounds. Ether Dome.

12 m. Massachusetts General Hospital. Clinical-Pathologic Conference.

*Open to the medical profession.
†Open to Fellows of the Massachusetts Medical Society.

January 7—Joint Meeting of the Boston Council of Social Agencies and the Boston Health League. See page 1259.

January 10 - March 21—Sunday Afternoon Lectures at the Harvard Medical School. See page 1141, issue of December 10.

January 14—Pentucket Association of Physicians. Hotel Bartlett, 95 Main Street, Haverhill, at 8:30 p. m.

January 15—William Harvey Society, 8 p. m. in the Auditorium of the Beth Israel Hospital, Boston.

January 15—Boston Society for the Advancement of Gastroenterology. See page 1145, issue of December 10.

January 20—Illustrated Lecture at the Robert B. Brigham Hospital. See page 1256.

February 3—American Social Hygiene Association. See page 1186, issue of December 17.

February 25, 26, 27—The New England Hospital Association. Hotel Statler, Boston.

March 30 - April 2—First International Conference on Fever Therapy. Postponement notice. See page 52, issue of July 2.

April 21-24—American Society for Experimental Pathology. See page 1075, issue of May 21.

October 25-29—American College of Surgeons. Chicago, Illinois.

DISTRICT MEDICAL SOCIETIES

ESSEX SOUTH DISTRICT MEDICAL SOCIETY

January 6—Meeting at the Danvers State Hospital, Hathorne, 5 p. m.

FRANKLIN DISTRICT MEDICAL SOCIETY

Will meet at the Weldon in Greenfield at 11 a. m. the second Tuesdays of January, March and May.

CHARLES MOLINE, M.D., Secretary.
Sunderland.

MIDDLESEX EAST DISTRICT MEDICAL SOCIETY

January 13—Bear Hill Golf Club, Stoneham.
March 16—Danvers State Hospital, Danvers.
May 11—Bear Hill Golf Club, Stoneham.

KENNETH L. MACLACHLAN, M.D., Secretary.
1 Bellevue Avenue, Melrose.

NORFOLK DISTRICT MEDICAL SOCIETY

January 19—8:15 p. m. The Peter Bent Brigham Hospital. Communications and Case Presentations by the Staff. Suggested title—"Abdominal Pain from the Medical and Surgical Standpoint." Details of program to be announced.

February 23—Time, place and details of program to be announced.

March 30—8:15 p. m. New England Deaconess Hospital. A Symposium on Diabetes entitled "A Survey of the Diabetic Work of the George F. Baker Clinic in the New England Deaconess Hospital." Communications and Case Presentations by the Staff. Drs. Elliott P. Joslin, Howard F. Root, Priscilla White, Alexander Marble and Allen P. Joslin.

May—Annual Meeting. Details to be announced.

Note: The Censors will meet for the examination of candidates on the first Thursday of May, 1937. Fee of $10.00 is payable at the time of examination. Application blanks may be obtained by writing the Secretary, furnishing name, address and name of school of graduation in medicine. Application must be made at least three weeks prior to date of examination. Candidates whose applications are on file will receive proper notices.

FRANK S. CRUICKSHANK, M.D., Secretary.
1247 Beacon Street, Brookline.

PLYMOUTH DISTRICT MEDICAL SOCIETY

January 21—11 a. m. Bridgewater State Farm.
March 18—11 a. m. Brockton Hospital.
April 15—Annual Meeting. 11 a. m. Ducy Hospital.
May 20—11 a. m. Lakeville State Sanatorium.

FRED F. WEINER, M.D., Secretary.
231 Main Street, Brockton.

SUFFOLK DISTRICT MEDICAL SOCIETY

January 27—Boston Medical Library. 8:15 p. m. Joint Meeting with the Boston Medical Library. "Anthropology." Dr. Carleton S. Coon.

March 31—Boston Medical Library. 8:15 p. m. "Social Insurance—It Affects the Medical Profession." Dr. Charles E. Mongan. Discussion: Dr. Channing Frothingham.

April 28—Annual Meeting. Boston Medical Library. 8:15 p. m. "Problems in Surgical Diagnosis." Dr. Howard M. Clute.

CONRAD WESSELHOEFT, M.D., President,
CHARLES C. LUND, M.D., Secretary.

WORCESTER DISTRICT MEDICAL SOCIETY

January 13—Worcester City Hospital, Worcester, Mass. 6:15 p. m.: Dinner—complimentary by the hospital. 7:30 p. m.: Business session and scientific program.

February 10—Worcester State Hospital, Worcester, Mass. 6:15 p. m.: Dinner—complimentary by the hospital. 7:30 p. m.: Business session and scientific program.

March 10—The Memorial Hospital, Worcester, Mass. 6:15 p. m.: Dinner—complimentary by the hospital. 7:30 p. m.: Business session and scientific program.

April 14—Worcester Hahnemann Hospital, Worcester, Mass. 6:15 p. m.: Dinner—complimentary by the hospital. 7:30 p. m.: Business session and scientific program.

May 6—At 4:30 in the rooms of the Worcester Medical Library, Inc., at 34 Elm Street, Worcester, will be held the spring meeting of the Board of Censors.

Wednesday Afternoon and Evening, May 12—Annual Meeting. Time and place for this meeting will be announced in an early spring issue of the Journal.

ERWIN C. MILLER, M.D., Secretary.
27 Elm Street, Worcester.

WORCESTER NORTH DISTRICT MEDICAL SOCIETY

January 27—Meeting at the Leominster Hospital, 4:30 p. m.

BOOKS RECEIVED FOR REVIEW

Applied Dietetics for Adults and Children in Health and Disease. Sanford Blum. 408 pp. Philadelphia: F. A. Davis Company. $4.75.

Chronic Indigestion. A Layman's Handbook. C. J. Tidmarsh. 143 pp. Toronto, London, New York: Longmans, Green & Company. $1.50.

William Withering. The Introduction of Digitalis into Medical Practice. Louis H. Roddis. 131 pp. New York: Paul B. Hoeber, Inc.

The Diagnosis and Treatment of Pneumonia. Campbell P. Howard. Edited by Henry A. Christian. 373 pp. New York: Oxford University Press.

The Diagnosis and Treatment of Chronic Diseases of the Respiratory Tract. With Especial Reference to the Lesions of the Trachea, Bronchi, Lungs, Pleura and Diaphragm. Elmer H. Funk. Revised by Burgess Gordon. Edited by Henry A. Christian. 618 pp. New York: Oxford University Press.

Plastic Surgery of the Nose. J. Eastman Sheehan. Second Edition, Entirely Rewritten. 186 pp. New York: Paul B. Hoeber, Inc. $9.00.